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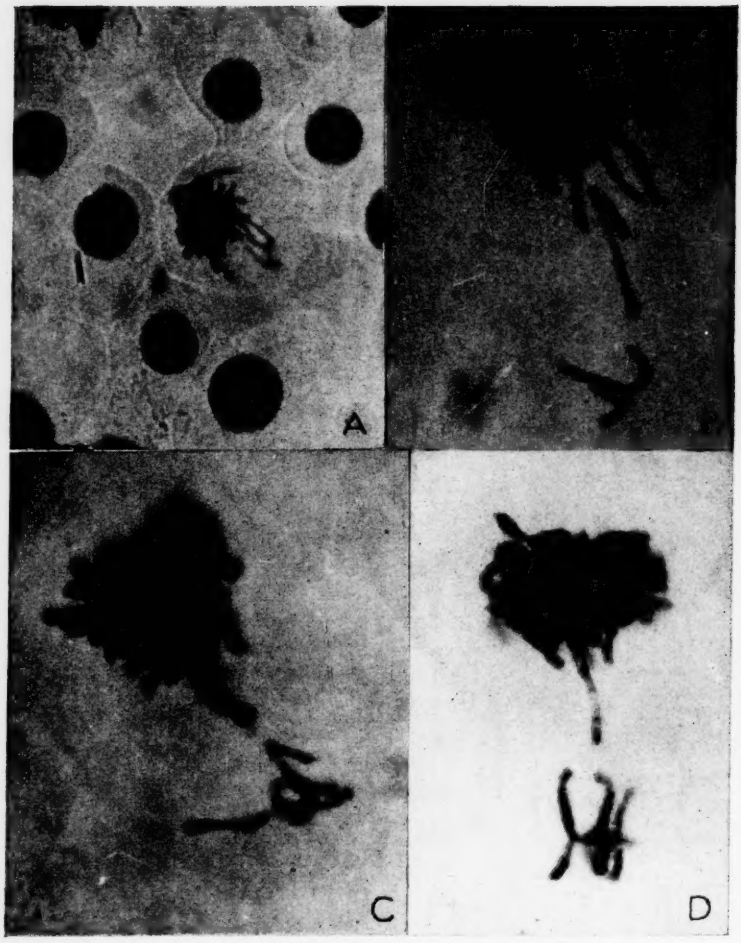

SODIUM NUCLEATE UPSETS MITOSIS
(SEE PAGE 327)

Genetics and Schizophrenia

Segregation and Reduction in Somatic Tissues

VOLUME 39 NOVEMBER, 1948 NUMBER 11

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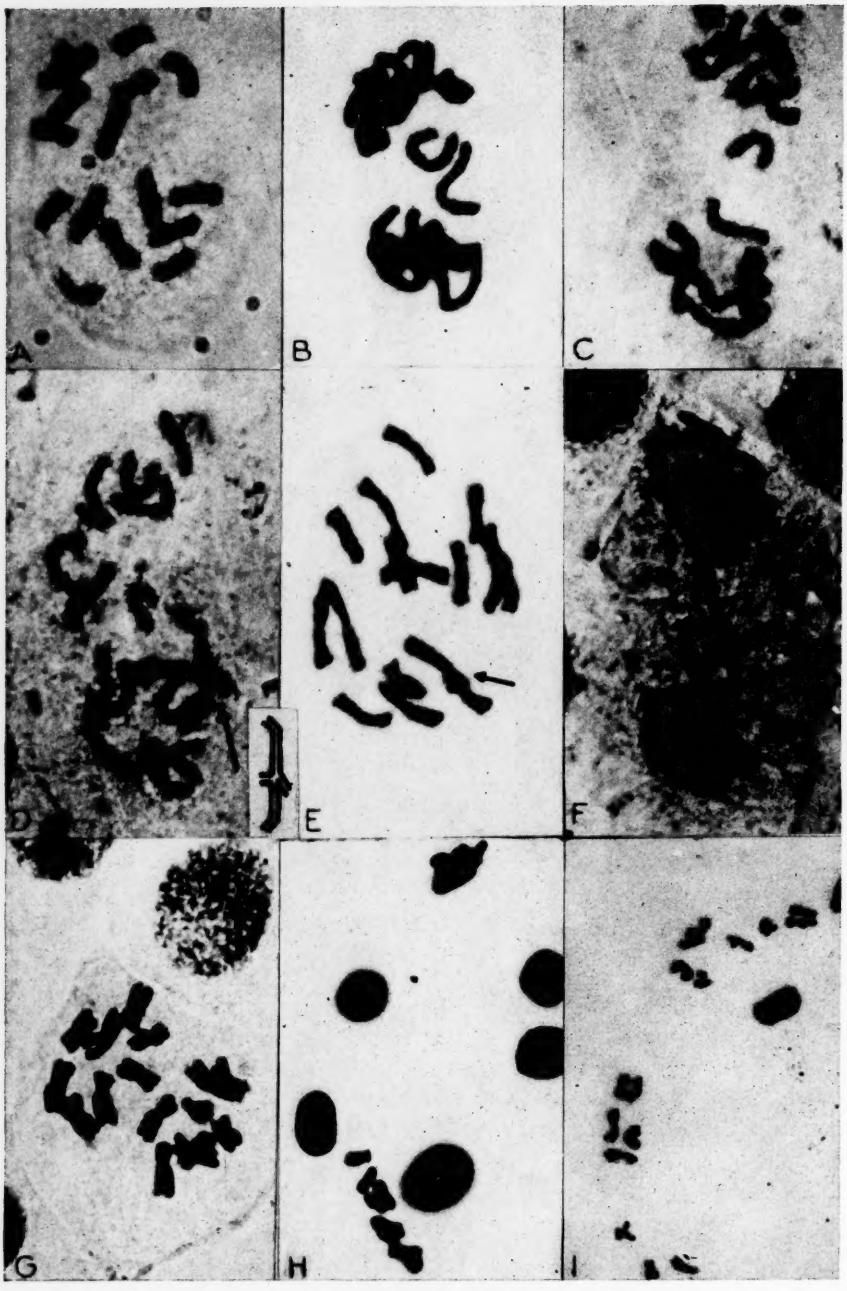

"SOMATIC MEIOSIS"

Figure 1

Photomicrographs of Root-tip cells of *Allium cepa* treated with sodium nucleate showing the equivalent of a meiotic first division; squash preparations. *B, C, D,* and *F* aceto-carmine, remainder Feulgen stained. *A-G, ca* 1300×; *H-I, ca* 600×. Description in text.

SEGREGATION AND REDUCTION IN SOMATIC TISSUES

I. Initial observations on *Allium cepa*

C. LEONARD HUSKINS
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IN the course of studies of chromosomes in differentiated regions of the roots of *Rhoeo discolor*[28] two haploid cells and two nuclei having chromosome catenations, similar to those characteristic of its pollen mother-cells, and apparently undergoing meiosis were found. Two haploid cells were also found in *Allium* roots. These *Rhoeo* and *Allium* plants had been treated with indole-3-acetic acid, but there is no reason to suspect that it induced the chromosome reduction (contra Mather[36]). A haploid cell was also found in untreated *Paphiopedalum* (Duncan, unpublished). Later,[23] reduction-divisions and haploid nuclei were found in considerable numbers in roots of onion bulbs growing in water containing 1-4% sodium nucleate. In subsequent extensive studies of the effects of sodium nucleate, somatic reduction has been found to occur occasionally in the controls in several different species of plants, and with fairly high frequency in roots from some wilted onion bulbs that had been kept on a laboratory shelf all winter. These findings have demanded an examination of the literature for other cases of somatic reduction, or data that could be so interpreted, and seem to warrant a preliminary assay of its possible wider occurrence and significance.

Berger[5] showed that somatic reduction is a regular feature in the ileum of mosquito larvae. His report was received with considerable skepticism (see [6]) but has since been confirmed and extended by Grell[19, 20] who has also clarified certain details in the process. The sporadic occurrence of reduction in somatic nuclei has been noted in various plants and animals by a number of workers. Gates[18] observed reduction-divisions in the nucellus of *Oenothera lata* and from conversations it appears that many cytologists have observed them in this tissue in various plants, as I did in *Matthiola incana* in 1930. Few such observations have been published because they are rarely "well-fixed" and are therefore usually dismissed as of doubtful validity. The occurrence of reduction is recorded in many cytological studies of mammalian tumors, but again with varying degrees of validity on account of the frequent clumping of chromosomes and of irregularities of many kinds in such material. Unpublished reports of haploid nuclei in *Paphiopedalum* roots and of reduction-divisions in roots of brome grass have recently been received from R. A. MacLeod and I. W. Knobloch respectively.

Battaglia[2] has recently shown that in *Sambucus Ebulus* L. "the somatic cells constituting the basal portion of the style tissue . . . undergo an usual [sic] heterotypic division with formation of bivalents and binucleate cells [two haploid nuclei]". Christoff and Christoff[10] have found that in *Hieraceum hoppeanum* "an unusual reduction-division [occurs] in the integumental cells, which is influenced by some external factors." It results in plants with 45 chromosomes arising from one with $2n=90$.

The most completely analysed case of somatic reduction in plants is that recorded recently by Brown[8] in cotton. In this instance it seems that the cytogenetically unbalanced nature of the parent polyploid plant favored the development of a reduced tissue. There seems little doubt that reduced cells occur not too infrequently in many plants but that they rarely form flowering branches or large segments. Wink-

ler's[58] *Solanum darwineanum** which is usually cited as the classical case of somatic reduction is not so listed here nor are early inconclusive accounts of reduction in Amphibian tissues. On the other hand, some of Nemec's[42] early reports of reduction following chemical treatments might perhaps be worth reinvestigation.

Premeiotic reduction as a regular feature in a portion of the hermaphrodite gonad was established by Hughes-Schrader[21] in the coccid *Icerya purchasi.* She found no chromosome pairing or heterotype divisions preceding the appearance of haploid nuclei and was unable to suggest a mechanism for reduction. But she pointed out that in *Pseudococcus* and *Lecanium* there is a perfectly regulated segregation at anaphase without any prior synapsis and that Metz[38] had shown regular segregation in *Sciara* "without any previous pairing, synapsis, or even any alignment in an equatorial plate stage." She noted that the appearance of haploid nuclei is concomitant with degeneration of many diploid nuclei. These observations may bear on the experimentally induced reduction-divisions reported below.

In an interspecific *Sciara* hybrid Metz[39] found a mosaic salivary gland in which some of the nuclei had chromosomes of only one of the parental species. The segregation had apparently taken place a few cell generations before the final mitosis in the gland.

It seems strange that with all these cases of reduction noted in the literature (and doubtless many more would be found were a more thorough search made) more extensive consideration has not been given to their possible bearing on such questions as the reversal of polyploidy, the origin of sexuality, unusual cases of segregation, somatic "mutation," etc. Some of the possibilities have been mentioned elsewhere.[23] Consideration of them in fuller detail may profitably be deferred until more data are available from the experimental methods now at hand for increasing the frequency of somatic reduction and segregation, but they should certainly be borne in mind. Re-reading of Bateson's papers, particularly his last,[1] may be salutary in this regard. It shows that a major factor in his hesitant and incomplete acceptance of the chromosome theory was his conviction that: "Though . . . segregation is commonly effected at the reduction-division, evidence steadily accumulates showing that at least in plants of many kinds comparable segregations occur in somatic divisions also." And again: "Somehow a somatic cell is evidently able to divide in such a way as to produce cells dissimilar either from the parent cell or from each other or both." He warned that "to speak of all such sports as 'mutation' . . . is likely to introduce confusion." Though other explanations than somatic segregation have been found for some of the cases that troubled Bateson. most of them have been ignored or forgotten during the past quarter century when it has been fashionable in some schools of cytogenetics to ignore rather than to "treasure your exceptions" as he advised (*cf* Schrader[48]). That Bateson could not envisage somatic segregation in terms of chromosomes, as we can, is not surprising in view of the opinion then fairly widely held (and cited by him from Strangeways) that "the chromosomes . . . disappear altogether after telophase and pass into solution." Further, he accepted the cytologist's dictum that in the developing zygote "whatever the resulting tissue, its chromosome content is the same." How could he reconcile his evidence of somatic segregation with these cytological concepts? We now know: (a) that the chromosomes do not dissolve at telophase and (b) that quantitatively the chromosome constitution is not the same in all cells.[27,28] Further, we now have serious reason to suspect that chromosome segregation in somatic tissues may be of widespread occurrence.

*It was a "graft-hybrid"; the parents (or rather, parental components) had $2n=24$ and 72. The sub-epidermal layer had 48 chromosomes; Winkler's assumption was that two parental nuclei fused to give one with 96 chromosomes which had then undergone reduction to give the cell-layer with 48. Endotetraploidy in the diploid component now seems more plausible.

Jones[29,30] also has emphasized that many variations in maize endosperm which earlier were described as somatic mutations, may actually be due to segregation. He interprets much of his later evidence[31] as indicating translocations, deficiencies, etc., rather than regular somatic crossing-over. It is possible, however, that, like Bateson earlier, his interpretations have been limited by the cytological picture available to him. Negatively, we have, of course, to discount the concept which he cites from Weatherwax, that the nuclei of the endosperm commonly undergo "direct," i.e., amitotic, division. Then, to current cytological evidence of the widespread occurrence of polysomaty, somatic segregation and reduction, there has to be added the fact that in the later stages of development of the maize endosperm its nuclei are polytene (Duncan[16]). This latter provides an obvious mechanism for the delayed appearance of the effects of segregation, which apart from polyteny must be a complex process in a triploid tissue. Further discussion of Jones' invaluable genetic data or of McClintock's various beautiful and precise cytogenetic analyses of the behavior of maize chromosomes, would, however, be beyond the scope of the present paper.

Genetic evidence of somatic reduction is given in the well-known work of Bridges[7] relative to sex-determination in Drosophila, but this was considered due to the maternal chromosomes being unable to "maintain the normal division-pace." Evidence of crossing-over and segregation in somatic cells was given by Muller[41] in an early paper on "The Mechanism of Crossing-over." He showed that 100% of the offspring of a certain male fly were crossovers and that the crossing-over must have occurred in an early embryonic cell that was ancestral to both somatic and gonial tissue. There was no evidence of haploidy accompanying the segregation; on the four-stranded crossing-over concept, two crossover chromatids must have segregated into a nucleus destined to become ancestral to spermatogonia and two non-crossover chromatids into somatic cells, with all nuclei remaining diploid. Much other evidence of somatic crossing-over in Drosophila is given by Stern,[51] Whittinghill[54] and others. "Somatic pairing" or association of homologues occurs regularly in the Diptera and this has tended to create an impression that somatic crossing-over in Drosophila is a special case and perhaps the only one for which a definitely known mechanism exists; the evidence does not warrant this conclusion. The "somatic pairing" described in many plants by numerous authors (see Watkins[53]) will not be considered in detail here since the value of the evidence for it varies greatly in different cases. It is, however, of interest to note Strasburger's[52] insistence that in plants attraction of chromosomes occurs only in pairs and not between higher multiples. This is not true of the Diptera.[37] The definite association of non-homologous somatic chromosomes through interchanges of chromatids as found by Peto[45] is a distinct issue, though he termed them chiasmata. They are apparently due to random breakage and fusion under the influence of the chloral hydrate treatment. Doubtless this was involved in some of Nemec's results also.

Gonomery should also be disregarded here, though it gives superficially similar cytological appearances. Where it occurs, the two parental genomes may remain distinct within the one nucleus and mitoses similar in appearance to some of those shown herein therefore occur regularly. But as Wilson[55] pointed out, it is found "only in the earlier stages of development" and it "represents no more than a tendency on the part of chromosomes to remain in separate maternal and paternal groups." This tendency is soon lost and "chromosomes of maternal and paternal ancestry become intermingled as development proceeds." Gonomery, therefore, can assuredly have no significance in causing the onion reduction figures since these cells are removed by many mitotic cycles from the original zygote. Even more does this hold for similar figures obtained in *Tradescantia* nuclei which have

a very long history of vegetative reproduction. To settle this matter experimentally, and the related one of possible genome segregation, a report will be published shortly of a study which has been made on an orchid hybrid in which six of the maternal and paternal chromosomes can be distinguished.

In a 42-chromosome wheat plant that was an F_7 from a pentaploid hybrid, Love[35] found two pollen mother-cells that had undergone "premeiotic" reduction and whose 21 chromosomes were undergoing a second, ordinary meiotic, reduction. One of these cells had $7_{II} + 7_I$ and could therefore have produced either one or two 7-chromosome, ancestral-type gametes.

Either somatic or gonial reduction followed by gonocyte meiosis or a gametophytic reduction following the latter could account for cases such as (1) East's[17] recovery of a 7-chromosome ancestral-type gamete from a 42-chromosome strawberry, (2) Nishiyama's[43] diploid oat resembling *Avena strigosa* from a pentaploid hybrid of *A. fatua* × *A. barbata,* (3) Kiellander's[32] 18-chromosome *Poa* resembling *P. trivialis* from a 72-chromosome *P. pratensis* and other such. It is probable that many such cases are known to workers with polyploids. They have not usually been emphasized because in most cases the possibilities of contamination with foreign pollen or accidental admixture of seeds cannot be ruled out as they were by East and Nishiyama. There are doubtless also many more unpublished cases for, as with cytological data above, several have been communicated to me personally since the first announcement[22,23] of this work was made. Dr. A. H. Sparrow has kindly drawn my attention to three cases recorded in his M.S. thesis.[50] These were 28-chromosome plants arising in a 42-chromosome hybrid wheat line. They regularly formed 14 bivalents.

General Remarks and Acknowledgements

It has long been obvious that nucleic acids must play some very significant role in chromosome mechanics; the speculations on this role are too numerous to cite. The most clear-cut data and forthright conclusions were given by Caspersson.[9] He showed that the spermatogonia in a grasshopper are "nucleic acid-poor" and the primary spermatocytes "nucleic acid-rich." The synthesis of nucleic acids is completed before chromosome contraction in meiosis and it seems to have been synthesized in the spermatocyte nucleus as there is no appreciable amount of it in the cytoplasm or testicular fluid during the time so many cells are developing so quickly. He concludes: "These facts make it probable that nucleic acid plays a role in the synapsis or in the division of chromonemata or in both."

As part of a research program[22,23] which aims, in general terms, to combine the methods of "experimental cytology" with those of cytogenetics, various experiments with ribose nucleic acid, sodium nucleate and various components of nucleic acids were planned and the materials for them obtained in 1946-7. Dr. M. Kodani, who was with us temporarily during October and November 1947 as a Project Associate, was encouraged in his desire to determine their effects on onion roots. His prime interest, arising from some of his earlier studies,[33,34] was to compare their effects on root growth and on chromosome structure with those of a salivary-gland extract; mine, following Caspersson's "lead," was on their possible effects on chromosome reproduction and synapsis. As not uncommonly happens in cytology, we both found what we were looking for.* Dr. Kodani is publishing separately his observations on root growth, the production of "lampbrush" and condensed "meiotic-like" chromosomes and on irregularities of chromosome beha-

*Consider Miescher[40] speaking of a more "exact" science: "Alles, was man finden will, muss man zuerst voraussetzen und vermuthen"—an overstatement, one hopes, but a useful corrective to the idea that it is necessary only to "describe what you see."

vior and distribution. Herein are the observations, the first of which were made on Dr. Kodani's slides, which convinced me that one of the effects of sodium nucleate is the production of an effective, albeit in part unusual, type of reduction-division that may provisionally be termed "somatic meiosis."

It must be emphasized that it was immediately recognized that *Allium cepa* is unfavorable material for establishing definitely the detailed process of "somatic meiosis" and its results. This species has eight pairs of chromosomes of which at most, five can be individually identified, and those almost always very doubtfully; and it is not favorable for genetic tests. Several experiments on different plants were started immediately, and Dr. Kodani planned one on Drosophila but was obliged, owing to a prior commitment, to leave for Japan. At the meetings of the Genetics Society in Chicago, December 28, 1947, the preliminary observations on *Allium, Tradescantia,* and *Rhoeo,* the latter with catenations in treated root-tip nuclei similar to those of its normal pollen mother-cells, were demonstrated. Cytological, cytochemical and cytogenetic tests of the effects of nucleates and their components and of amino acids on the nuclei of various plants and animals are now being made by our research group. These probably color to some extent the interpretation of the *Allium* data here presented, but they will be offered separately and as far as possible independently.

This will necessitate giving an apparently hesitant and tentative interpretation to some of the *Allium* figures that in the light of fuller knowledge from other materials could be interpreted more boldly. If this results in a presentation that does not carry complete conviction it may, as a corollary, show why naturally occurring somatic reduction-divisions have so generally been overlooked. Many cytologists must have seen, in untreated roots, figures like many of those herein, and, quite properly, decided not to attribute significance to them. Only when they are found repeatedly and their details correlated do they mean anything. Certainly such a presentation will show the necessity for diverse experiments on various organisms if all details of the process are to be elucidated. *Rhoeo,* for instance, being a translocation heterozygote, will give evidence on the specificity of pairing. At the same time it may help clarify the role of heterochromatin in somatic association. *Crocus* gives evidence on "distance conjugation" without which some of the *Allium* observations seem inexplicable. *Trillium* and *Crocus* both give evidence on the specificity of the repulsion between homologues. The tomato is favorable for cytogenetic analyses. The irregularities of mitosis that are found in many of the treated nuclei will not be considered here since they are being described independently by Dr. Kodani. It seems at present that in their effects on chromosome reduction, nucleic acids are different in kind from many mitotic poisons, such as colchicine, acenaphthene, ethylene glycol, chloral hydrate, etc., while in the production of various irregularities, many of which are simply necromorphisms, in part due to over-dosage, they may be similar.

I am particularly indebted to Dr. Kodani for the use of the initial preparations and to Dr. Lotti Steinitz, Dr. Rhona Leonard-Bennett, Marianne Weisz, Norah Stewart, Dr. Irving Galinsky, R. P. Patil, and Walter Drapala for making subsequent treatments and from them sectioned and squash preparations. Replicated tests of six samples of sodium nucleate were also made by 12 students as a class exercise. To Dr. G. B. Wilson I am indebted for recent help in examining preparations and selecting nuclei for illustration, to Dorothea Voss-Helmen for help with drawings and to Alfred Owczarzak with the photomicrography.

Methods

The method, used initially by Dr. Kodani, is simply to grow onion bulbs in tap water and then to place them with their roots in a solution of ribose nucleic acid or its sodium salt, in distilled water. The sodium nucleate has simply the ad-

vantage of greater solubility. Concentrations ranged from 0.5% to 8.0% and period of treatment from 3 to 36 hours. For the onion the optimum is probably between 1 and 2% for 6 to 12 hours, but it seems that this varies greatly with the condition of the bulbs and growth-rate at the time of treatment. In some treatments the pH was adjusted to neutrality, usually with NaOH. It may be added that different plants will tolerate, and require for an effect, very different concentrations.

Some good results have been obtained with excised roots placed in water or culture solution to which sodium nucleate has been added. With some plants injection and spraying the leaves have both been effective. Standardized methods have yet to be developed and the role of the components of nucleic acid and their interactions with certain other substances in the cell have yet to be determined.

The sodium nucleate used on onions was obtained from the Schwarz Laboratories, Inc., New York. It is made from yeast and is not critically purified. Since it can scarcely be imagined that the complicated processes of meiosis are specific effects of any one chemical substance, the lack of purity was no disadvantage in the initial studies reported herein. Six small and one large sample from Schwarz have been tested since the results obtained with the original lot (S.N. 4509) were first reported.[23] All eight samples cause chromosome segregation, but there seems to be less pairing with the latest large sample (S.N. 4704) than with the first. On the other hand, this may be due to other variables, not ignoring subjective ones. The six small samples did not permit any quantitative evaluation of their effects.

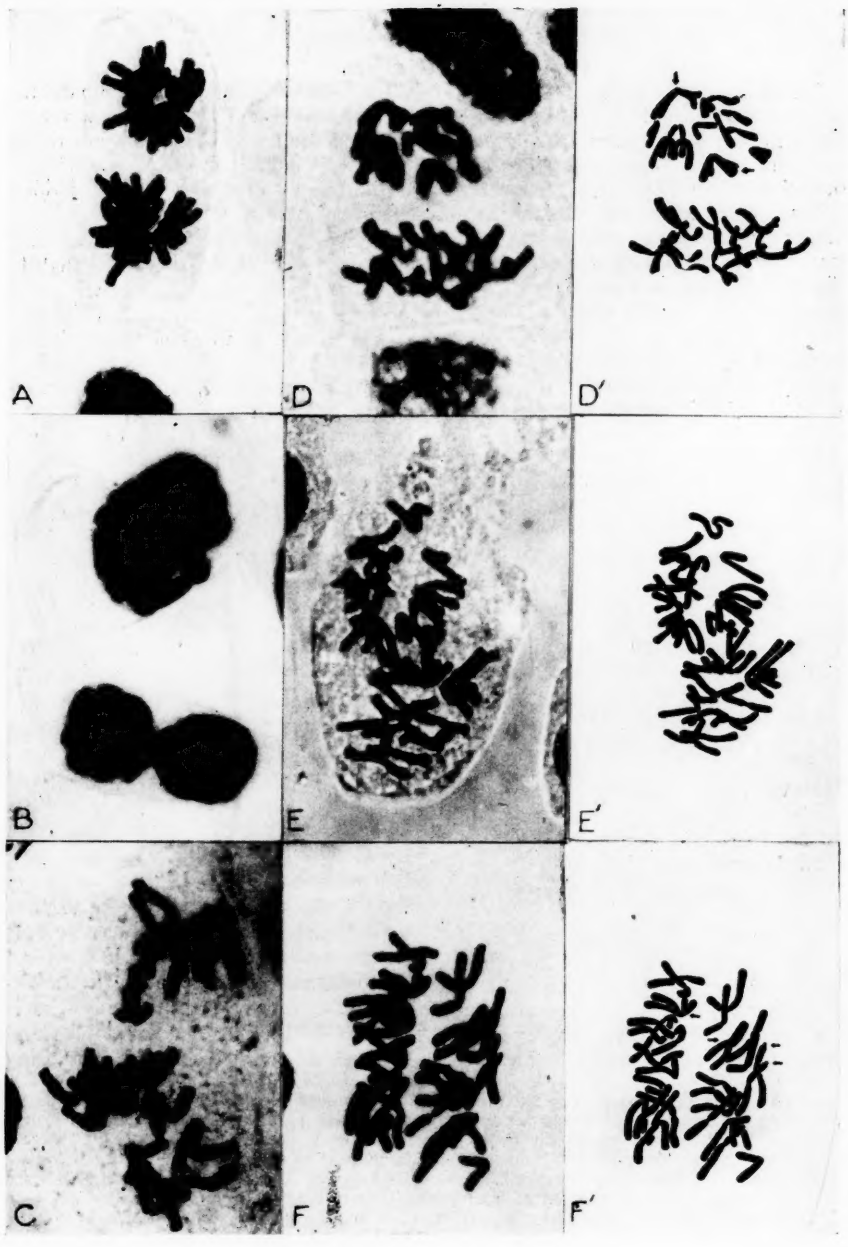
Sectioned material has been used to only a very limited extent, since essential details of chromosome structure are much more favorably shown in squash preparations of root tips fixed in 3:1 alcohol-acetic, hydrolyzed with H Cl and stained with Feulgen or aceto-carmine.

Observations

Many of the nuclear divisions in the meristem of treated onion roots seem to be completely ordinary, normal mitoses. A considerable proportion show unusual features, such as shortened and thickened chromosomes, but appear to be dividing regularly. A few show grossly abnormal chromosome distributions and others have "lampbrush" chromosomes. A reductional type of division occurs in not less than 2% of all mitoses in some experiments. A maximum cannot be stated since many division figures, naturally, cannot be interpreted with certainty—see below. In most of the "somatic meioses" the cells appear to be in a normal, healthy condition.

The frequency with which miscellaneous irregularities occur is directly related to dosage and length of treatment and can be predicted from the degree of flaccidity of the roots before fixation. In roots that appear turgid and healthy when fixed, the chromosomes almost all have a normal appearance; they are not clumped, fused or ragged in outline as after many chemical treatments. In general the cytological impression in healthy looking roots that have a high proportion of reducing divisions is one of disturbance within the range of viability or "normality." It is, therefore, particularly interesting to note that several of the features which are unusual (and therefore "abnormal") for the onion, resemble normal features of mitosis or meiosis in other organisms.

Separation of 16 condensed chromosomes, that look like meiotic univalents, into two groups of 8, as in Figure 1*A*, can be found in a number of cells; to decide whether in any one case it is a significant grouping or a chance result of pressure in making the squash preparations may be more difficult. Groups of eight in two successive sections have twice been found; this may seem more convincing than evidence from squash preparations, but the latter method has advantages for the determination of exact numbers and of chromosome structure.



SECOND DIVISION "MEIOSES"

Figure 2

Root-tip cells of *Allium cepa* treated with sodium nucleate showing the equivalent of a second meiotic division and the overlapping of two divisions. *A* and *B*: Cells with two haploid nuclei; *C-F*: the overlapping of two divisions in "somatic meiosis"; *E*, Upper group at mid-anaphase II, lower group at early anaphase II. See text for details. *D′*, *E′* and *F′* are drawings interpreting *D*, *E* and *F*. All *ca* 1300×. Squash preparations, *C* aceto-carmine, remainder Feulgen.

Actually, in the present study, the first evidence convincing to me came from incomplete separations such as those shown in Figures 1*B*,*C*, and *D*. In each of these there are seven chromosomes at each side of the cell and two of similar size and shape seem to be in process of separating from one another. In Figure 1*D* this eighth pair appears to be associated by a sub-terminal chiasma. Certainly the configuration would be so described by many cytogeneticists if seen in a meiocyte and it would be interpreted as in the accompanying line diagram.* There is no indication of any prior chiasma formation between the members of the eighth pair in Figures 1*B* or *C*. Neither has any sign of a spindle been seen, though Fast Green has been used with some of the Feulgen preparations. However, this aspect of the problem is now receiving special attention.

In Figure 1*E* two chromosomes of different size are united by an almost terminal chiasma. In another cell a median chiasma united two such chromosomes. The significance cannot be judged without a study of normal meiosis in the same plant. If the two chromosomes are "heteromorphic homologues" and have a region in common, the chiasma could be the result of crossing-over, but such configurations can also result from irregular breakage and reunion of chromatids.

In a number of cells, chromosomes of similar shape and size have been found lying together in pairs without chiasmata joining them, but "somatic pairing" cannot be studied satisfactorily if homologues cannot readily be identified.

In Figure 1*F* there are apparently eight chromosomes at one pole, seven at the other and one lying between them. The cell is intact but slightly constricted at the middle as if about to be divided by furrowing.

Figure 1*G* shows a cell in which two groups of eight chromosomes lie slightly separated from each other. Each chromosome has its chromatids widely separated except at the kinomere and resembles a typical metaphase II dyad in pollen mother-cell meiosis, or a "c-pair" resulting from treatment with colchicine. In their grouping they look like meiosis II plates; such groupings are, apparently, not commonly found after colchicine treatments. Figure 1*H* shows a group of eight dyads and far removed from them, with other nuclei in between, a condensed group that probably contains eight. Figure 1*I* shows a smashed cell in which there are also two groups of eight chromosomes well separated from each other. The number of smashed cells containing groups of eight chromosomes seems too high for random frequency and suggests that a cell with two such groups in it may be constricted and hence easily broken into two. Obviously no conclusions could be reached from such cells alone, but taken in conjunction with the next two figures they seem significant (see also Figure 3*F*). Figure 2*A* is an example of the binucleate cells which are interpreted as having two haploid metaphase II plates, i.e., as being a stage succeeding that in Figures 1*G* and *I*. Figures such as 1*G*, *H*, and *I* or as 2*A* could not alone carry any

*The topological and interpretative complexities involved in the correlation of cytological chiasmata and genetic crossovers are not always recognized, (*cf* Huskins and Newcombe[25] and Schrader[48]). The great advance in cytogenetic theory made possible by the brilliant analyses of Belling[4] and Darlington[13] has been to a considerable extent vitiated by subsequent uncritical work on chiasma frequencies, terminalization coefficients, etc. (including some by myself prior to 1935). Pending the completion of both genetic and cytological studies now in progress on other materials the only comment that will be made on the problem of chiasmata in somatic nuclei is the following: When pairing and segregation without chiasmata, such as that occurring in Figure 2, was first observed it was emphasized, because in no plant has gonocyte meiotic pairing and segregation without chiasmata so far been established (though some evidence for it even in *Trillium*[26] was presented in 1935). Now the evidence indicates that pairing with chiasmata is the exception in "somatic meiosis" induced by sodium nucleate and a change of emphasis, necessitating different experimental materials, has been found necessary. K. W. Cooper's critical analyses[11, 12] of the chiasma problem in the *Diptera* give an indication of the issues that have to be faced.

conviction; but the former permit recognition of chromosome shape as like that of typical metaphase II, while the latter shows clearly that there are two metaphase plates in one cell. In such plates there appear to be 8 bipartite chromosomes, similar to those of Figure 1*G*, but their crowding prevents clear identification as such. Figure 2*B* shows a binucleate cell in which the chromosome numbers cannot be determined definitely but there are clearly only about half as many in each nucleus as in that of the adjacent uninucleate cell. It cannot be determined whether this has resulted from separations such as those in Figure 1*G-I* or from such as 3*A-F*.

Figures 2*C-F* must be considered together and also in relation to Figure 1*G*. In Figure 2*E* and *E'* there are clearly two groups of about 16 chromosomes each. The lower group can be interpreted as at early anaphase and the upper at mid-anaphase, but figures somewhat resembling this can be found after treatment with various mitotic poisons. Figure 2*C* was the first to indicate in itself that a second division, similar in function to that of ordinary meiosis but differing in its time of onset may occur in these sodium nucleate treatments. In the lower half of this cell there are two groups of eight single chromosomes that appear to be separating from each other while in the upper half there are five bipartite and six single chromosomes. Unfortunately this preparation was lost or mislaid before it could be drawn. However, Figure 2*D* and *D'* shows an essentially similar cell excepting that the 16 single chromosomes in the lower half are not clearly separating into two groups of eight. In the upper there are twelve single chromosomes and two that are bipartite. In both groups single chromosomes of similar shape lie in pairs in many places. Figure 2*F* and *F'* shows what is interpreted as a complete overlapping of the two divisions of "somatic meiosis" and as such clarifies Figures 2*C* and *D* as partial overlaps. In it there are clearly two groups of 16 units each comprising eight pairs (the members of the second pair from the top in each group may actually still be united at the kinomere). Attention may be drawn to the constriction at the end of each member of the pair at 3 o'clock. This plant may have been heteromorphic for this chromosome, since none appears in the left-hand group, but we know from study of differential regions (*cf* Wilson and Boothroyd[56,57] *contra* Darlington and LaCour[15]), that too much significance must not be placed on variations in the appearance of such constricted regions. Its present significance lies in the evidence it provides that adjacent single chromosomes have been sister chromatids. The only apparent alternative to the interpretation of Figure 2*F* as a second division separation of chromatids during a first anaphase that is giving numerical reduction (we cannot from onion data conclude that segregation of homologues is occurring) would be that it is a mitotic metaphase plate that has somehow separated into two groups of eight chromosomes. Against this is, first, its general appearance and the unlikelihood of such a separation. In the fact that separation of chromatids is occurring last, instead of first, at the kinomere the pairs of associated single chromosomes (or chromatids) seem obviously to have been derived from bipartite chromosomes like those of Figures 1*G-I*. They thus resemble either typical meiotic metaphase II dyads or colchicine "c-pairs." But colchicine has not, so far as I know, been shown to give anaphase-like segregation coincident with dissociation of the "c-pairs."

Figures 3*A-F* show a condition not noticed during the first months' study of *Allium*. The chromosomes are separating into two groups during what look like various stages of prophase. Figure 3*F* and *F'* shows segregation of two groups of eight chromosomes that are contracted to a degree characteristic of very late prophase. Perhaps Figures 1*B*, *C* and *D* should also be interpreted as very late prophase segregations instead of as anaphases. Obviously, however, the standard terminology has little significance here—at least not until we have

definite data on the presence or absence of a spindle.

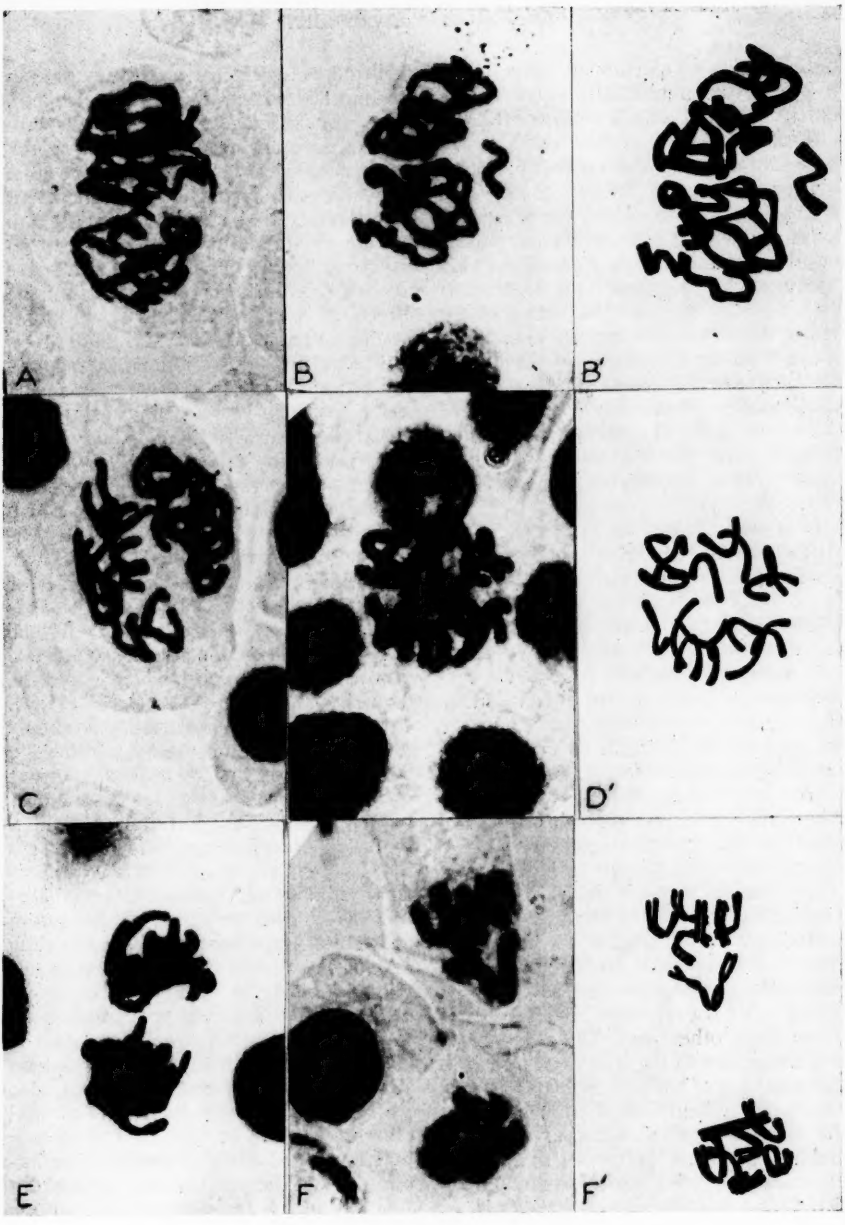
This type of prophase segregation was first noted in the water-poppy, *Hydrocleis nymphoides,* which Mr. Peter Nelson had given sodium nucleate treatments in concentrations of from 1-8%. He found no pairing or segregation such as shown in Figures 1*A*-2*F*. On one of his slides, however, I found five nuclei resembling that of Figure 3*A*. On checking back they were found in the onion slides also. They are now found far more frequently than any other type following treatment with sodium nucleate. This applies to 11 different plant species currently being studied. There is an obvious subjective factor involved, but there seems also to be more than that. Present indications are that sodium nucleate chiefly affects repulsion between chromosomes and, further, that it is the phosphorus constituent which is the effective agent (Galinsky). Chromosome pairing seems to depend upon some other nuclear constituent, preliminary indications from experiments with two amino acids being that they play a significant part in it. If so, the difference in frequency with which pairing and segregation of condensed chromosomes took place in the early experiments and prophase segregation in the more recent ones may be due to differences in the quantity of impurities in the samples of sodium nucleate and/or the water in which they were grown until treated. The tap water used in the early experiments had a high content of organic matter. On the other hand, growing conditions, growth rate and, with onions at least, the condition and age of the bulb all affect the results. These issues are currently all under investigation.

In Figure 3*A* the separation is 9 + 7 and in Figure 3*B* and *B'* it is 8 + 7 with the 16th chromosome at one side. In Figures 3*C, D* and *F* and most probably in 3*E* the segregation is 8 + 8, which is the commonest distribution. In a sample of 131 segregating nuclei Dr. G. B. Wilson has found 61 separations of 8 + 8, 52 of 7 + 9, 12 of 6 + 10, and 6 of 5 + 11 or more unequal separations. There is no plausible working hypothesis from which to calculate expectation but if 16 independent bodies went at random to either side of a cell the frequencies of the groupings expected would be 26, 46, 32, and 27. The data from *Allium* do not merit further consideration because many better data from other plants are now becoming available.

Discussion

Comparison with the cases cited in the first section of this paper shows that many of the unusual features found in these reduction-divisions induced in *Allium* roots resemble normal stages of mitosis or meiosis in other organisms. For instance, movement of chromosomes ends first, instead of with the kinomere leading, is found in *Sciara.* In the coccids, there is segregation without synapsis. In *Aggregata eberthii* Belar[3] showed that the mitotic chromosomes "split" and separate without condensing to the metaphase state, though not without a spindle. Only in having the combination of segregation without either synapsis, condensation, i.e., tight coiling, or a spindle do the *Allium* "prophase segregations" transcend the range of normality commonly known. From the present material one gathers the general impression that what is being revealed under the influence of the crude sodium nucleate we are using is the dissociation of various adaptive mechanisms which when superimposed on a basic repulsion inherent in the chromosome itself produce the complicated but normally closely coordinated meiotic process we recognize as "typical" for a flowering plant. Such a subjective impression has, of course, in itself little or no scientific value excepting insofar as it suggests test objects and stimulates researches which may give precise answers to some of the questions the present observations raise. We have undertaken many distinct tests and hope that others will initiate experiments with materials more familiar to them than to us.

Though the segregations might, so far as the evidence herein goes, be the result of random scattering they could still, of course, give segregation of complete



SEGREGATION AND REDUCTION

Figure 3

Root-tip cells of *Allium cepa* treated with sodium nucleate, showing segregation and reduction at stages apparently ranging from early to late prophase. See text for details. *B'*, *D'* and *F'* are drawings interpreting *B*, *D* and *F*. All *ca* 1300×. All are Feulgen-stained squashes.

genomes in a proportion of cases (e.g., *ca 2%* of the numerically equal distributions in onion with $n = 8$ and 12.5% in *Trillium* with $n = 5$). Doubling of these through the formation of second division restitution nuclei could give homozygous diploid cells in an otherwise heterozygous organism. In later papers on other organisms it will be shown that association and segregation is not at random. A way is therefore indicated by which, when we have further knowledge of the process and techniques developed, the plant breeders' work may be greatly accelerated at least with some types of plants (tomato callus seems particularly favorable for the extraction of recessives, by somatic segregation, from a heterozygote).

If somatic reduction occurs in polyploids and a reduced tissue forms in which sporogenous cells thereafter undergo ordinary meiosis, some gametes will be formed which are of, or approach, the ancestral-types. Alternately, gonocyte reduction may be followed by a second meiosis in the gametophyte. Either of these types of double reduction may be the method of origin of progeny resembling ancestral forms, such as occurred in the cases cited above. Various minor applications to plant breeding become possible to envisage, such as the transfer of genes from high to lower polyploids or diploids in cases where doubling of the lower form is difficult, or reduces viability or, if accomplished, gives too complex segregation. Reduction without crossing-over, as evidently occurs in most of these induced divisions, gives other possibilities.

Throughout all the studies so far made of the effects of sodium nucleate, the impression has held that it only enhances the frequency of variations of nuclear and chromosome behavior that occur naturally but with such low frequency that they are rarely detected. This is, of course, not surprising since nothing has been added to the cell that is not normally present. However, *in vivo* these nucleic acids are highly polymerized. In degenerating tissues they are probably depolymerized as in the Schwarz sodium nucleate. That nucleic acids vary greatly in concentration in different tissues and, as shown particularly clearly by Caspersson, in different parts of the cell during its division cycle is well known and was, of course, the starting point of the chain of reasoning that led to the decision to initiate such experiments. However, until more highly purified materials are available, it must be recognized that the effects of commercial nucleic acid might be due in part to impurities.

The pairing which, following Caspersson's "lead," we hoped to effect has been found so far in very few nuclei. Instead we find evidence to be added to that of Metz and many others that the chromosomes have in themselves a property of repulsion (as well as of attraction) which independently of any extraneous mechanism, such as a spindle, is effective in separating either whole chromosomes or their component chromatids. This has of course been recognized by all who have ever worked on the mechanism of mitosis, but the emphasis is new and the data should lead to new points of view. The repulsion is not attributable simply to a doubled state in the microscopically visible chromosome; there is no evidence of attraction in pairs and repulsion between pairs of paired strands (Darlington[14]) at the microscopic level (though that is of course possible at the molecular). This is particularly clear in Figures *2C-E,* where bipartite chromosomes and unitary chromatids are separating from each other at the same time in single nuclei. Again, while the kinomere obviously has a special role in chromosome mechanics it does not necessarily take the lead in moving the chromosomes apart from one another — see also Rhoades and Vilkomerson,[46] Metz[38] and others.

It is yet too early to evaluate the implications of the present data for the elucidation of the mechanisms of mitosis and meiosis in general, but it does seem obvious that they should lead the biophysicist to concentrate his attention on the chromosome itself rather than on other features of the mitotic process such as the spindle, astral rays, etc., which

seem clearly to be ancillary. The lack of success which has for so long characterized attempts to elucidate the mechanisms of mitosis (see Schrader[47]) through the use of models that simulate spindle and astral figures, metaphase plate-polar fields, etc., is not surprising if these are merely subsidiary factors. They are doubtless adaptive and help to ensure the regularity of the process but apparently can be dispensed with even in a highly evolved flowering plant, without necessarily destroying the functionally essential features of the meiotic process.

Östergren[44] states that "the property of being able to induce spindle disturbances (c-mitosis) is present in most organic substances" and also that many substances as well as X-rays and certain genes can induce chromosome stickiness. He shows that ethylene glycol is a particularly effective agent for inducing stickiness, and therefore chromosome mutations, because of its low toxicity. It must here be emphasized that though there are superficial similarities between some of the effects of sodium nucleate and many "mitotic poisons" an extensive examination of the literature has failed to produce evidence that any of the latter produce separation of the chromosome complement into two groups, with equal or nearly equal numbers in each, with anything remotely approaching the frequency found after sodium nucleate (or phosphates). If they do cause somatic reduction and segregation their significance in this regard has apparently been missed. Further, sodium nucleate in moderate dosage does not produce "stickiness" or any grossly abnormal appearance in the chromosomes, nor have we so far any evidence of mutation accompanying somatic segregation in our cytogenetic experiments. Yet again, it is clear from the occurrence of segregation at very early prophase stages that it is not disturbance of a normally developed spindle that is involved, as it is with colchicine, etc. In fact it is very doubtful if any ordinary spindle mechanism is involved even in the segregations of metaphase-like chromosomes, but a detailed study is needed before any definite statement is made on this issue.

Finally, it must be emphasized that the study here reported is merely the initial one in what must be an extended series (we hope by others as well as ourselves) before the issues it raises can be adjudicated. These issues currently fall into at least five categories: (1) the cytochemical; (2) the cytological including chromosome mechanics and, even if negatively, the spindle; (3) the cytogenetic effects including somatic segregation and possibly its relation to some cases that have been classed as mutation; (4) the cyto-evolutionary, for which wild forms or species already suspected of having resulted from reversed polyploidy are desirable — *Tradescantia* is the most promising form currently being studied; (5) the possible relation of somatic reduction to the origin of sexuality, for which a "primitive" organism will probably be necessary—this as yet has scarcely been considered. Further issues, if not further categories will, of course, arise as the work proceeds. Different experimental materials are needed for elucidation of the different issues. For instance, for (1), the cytochemical studies, micro-organisms or tissues in sterile culture are likely to be best after preliminary studies of plants in culture solutions are completed and significant "leads" obtained from them. It is obvious that a highly organized structure such as a plant root is not expected to be the most favorable for attempts to produce viable modifications of the mitotic process. It is a very convenient test object for first-level experiments and will suffice for the elucidation of many issues. For more thorough-going attempts to induce and control the meiotic process, less organized tissues, perhaps such as plant callus or animal tumor, or possibly micro-organisms, are indicated. For (2) organisms with individually distinguishable chromosomes and also with translocations, etc., are being used. For (3) a plant such as the tomato which reproduces from callus that can easily be treated with the reagents, was obviously indicated for the first tests; the *Grami-*

neae, which are most important from the plant-breeders' point of view, were expected to be among the most difficult, but by use of a chromosomally aberrant form of wheat some indication has been obtained that the problem may not be quite as difficult as anticipated.[24] Two experiments with tail tips of *Triturus,* kindly furnished by Dr. G. Fankhauser, have given no results.

Until more of the issues are settled, one hesitates either to call these reducing-divisions meiosis or to coin a new term for them. Etymologically, meiosis means only "to lessen." The term "elaxis," from Greek-diminution, has been adopted by Schreiber[49] for what he considers "a proportional and discontinuous reduction of nuclear size during ontogenesis" (perhaps this is through a diminution in the degree of polyteny). If it were not already preempted, elaxis would be a very satisfactory term. For the present these natural and induced somatic reduction-divisions will be termed "somatic meiosis" without, however, any implication that they necessarily involve all the essential features of the gonocyte meiosis of the organism involved.

Evidence is accumulating that somatic segregation and/or reduction occur not too infrequently under "natural" conditions. Figures such as 2*D-F* and the fact that few haploid nuclei are formed probably indicate the reason it has so generally been overlooked. If a haploid set of bipartite chromosomes is segregated to each side of the cell and they begin immediately to separate into their constituent chromatids particularly as in Figure 2*F,* or if two distinct haploid nuclei, as in Figure 2*A,* are formed but the second division is abortive, the diploid chromosome number is at once restored. Unless somatic reduction occurs fairly frequently it is therefore very likely to be missed by the cytologist unless the organism has grossly heteromorphic pairs of chromosomes. It will, however, be seen by the geneticist as somatic segregation when it occurs in a heterozygote. If the production of homozygous diploid tissues could be induced frequently enough, it would have some advantages and few disadvantages for the plant-breeder over the production of haploids.

Summary

By growing bulbs of *Allium cepa* in an aqueous solution of 1-4% sodium nucleate, chromosome segregation and/or reduction of the chromosome number has been induced in root-tip cells. In treatments of freshly harvested bulbs made November, 1947, with the Schwarz sample S.N. 4509 both pairing and segregation of metaphase-like chromosomes was obtained. A second division which separates sister chromatids and resembles that of a normal gonocyte meiosis occurred in a number of cells. More commonly the two divisions overlap and separation of chromatids occurs during the equivalent of gonocyte meiotic anaphase I.

Segregation of long, prophase-like chromosomes also occurs and this is the more frequent type of "somatic meiosis" found in both the onion and other plants in recent experiments with other samples of sodium nucleate. It has also been found in untreated onion bulbs that were flaccid after several months' storage at room temperature.

Some superficial similarities to the action of colchicine, ethylene glycol, etc., occur. The occurrence of "somatic meiosis" (either normally or by induction with substances that are used in the normal metabolism of the organism) raises many issues that require the use of different test-objects for their elucidation. Some of these are outlined. The onion data cannot present a complete picture but they indicate some of the lines along which further studies should proceed and in particular show that in an appreciable number of cells a process occurs that is genetically equivalent to gonocyte meiosis. In this the effects of sodium nucleate differ from those of "mitotic poisons."

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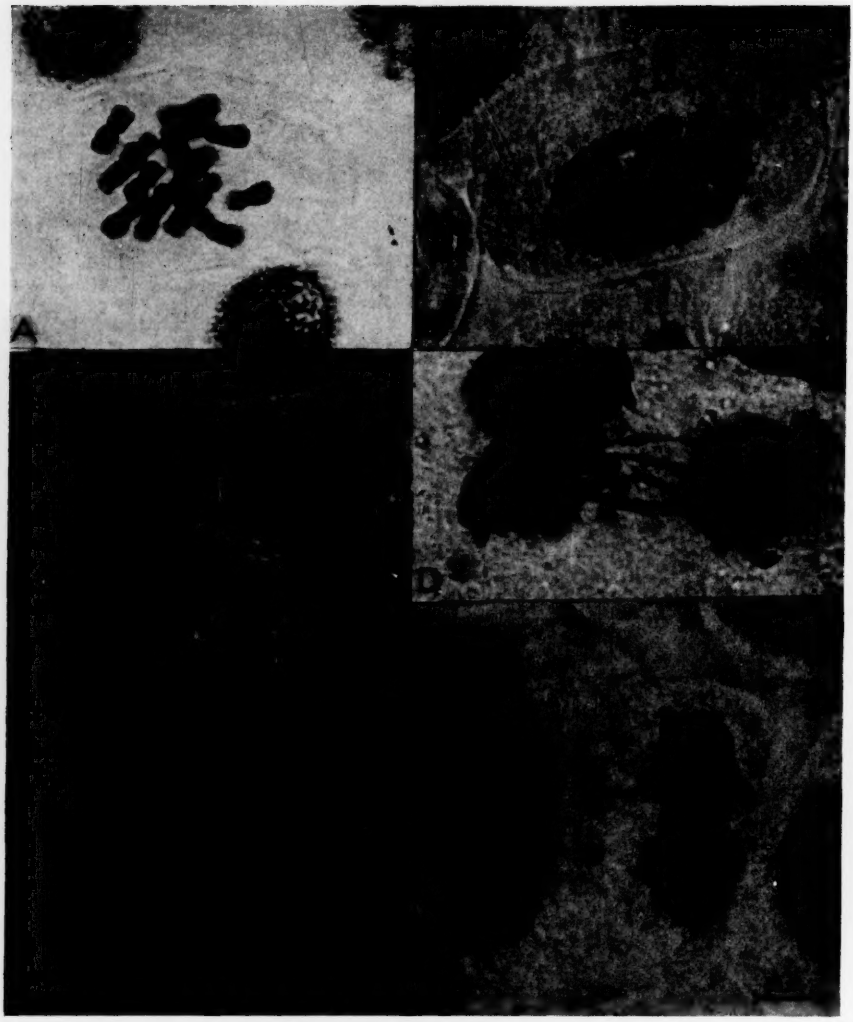

TREATED CHROMOSOMES

Figure 4

The effects of sodium ribose nucleate solutions on the chromosomes of the onion root meristem. *A*—Highly condensed chromosomes resulting from treatment with 4% solution for 12 hours. *B*—The metaphase chromosomes with the lampbrush structure (4%: 12 hours). *C*—Late anaphase with one lagging chromosome (4%: 16 hours). *D*—Four chromosome bridges are seen between the two groups of anaphase chromosomes (4%: 12 hours). *E*—Extremely condensed chromosomes after treatment with 8% solution for 12 hours; many chromosomes are spherical or nearly so; the nuclear membrane is still present and the chromosomes are all very close to it; note the lampbrush hairs. *F*—A chromosome fragment at the middle of the cell 4%: 16 hours). See text for details.

SODIUM RIBOSE NUCLEATE AND MITOSIS

Induction of Morphological Changes in the Chromosomes and of Abnormalities in Mitotic Divisions in the Root Meristem

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WHILE conducting experiments with ribose nucleic acid and other compounds containing nucleotides at the Department of Botany, University of Wisconsin, during October-November 1947, the author discovered that in onion root tips treated with solutions of the ribose nucleic acid of certain concentrations for certain lengths of time, the morphology of the chromosomes and their mitotic behavior are changed in many cells. He then undertook to investigate the induced changes under better controlled conditions. It is the purpose of this communication to report the method and results of this series of experiments and to discuss some of the important aspects of the results.

Bulbs of *Allium cepa* ($2n=16$) were set in tap water until a number of roots had grown to a length of a few millimeters. These bulbs were then set individually in vials filled with solutions described below in such a way that all roots and the basal parts of the bulbs were immersed in the solutions. Roots were then cut off at various time intervals and the meristems of these excised roots were fixed in 3-1 Carnoy's fixative for at least 15 minutes and then stained by the Feulgen method, and smeared. Some preparations were made by smearing with aceto-orcein. Both types of preparations were satisfactory for the present study. The photomicrographs presented in this paper were all taken from the Feulgen preparations.

Ribose nucleic acid is very slightly soluble in cold water. Therefore, in the later series of experiments sodium ribose nucleate was used, because of its greater solubility. The product of the Schwarz Laboratories, Inc., New York, N. Y. was used throughout the experiments. A series of eight solutions (in concentrations of 0.05, 0.1, 0.25, 0.5, 1, 2, 4, and 8 per cent) was made by dissolving appropriate amounts of the nucleic acid salt in cold distilled water. In one set of experiments, these solutions were used without being adjusted to the same pH. The pH of the distilled water was 5.8 and that of the 2% and 4% solutions was respectively 5 and 4.5. After 36 hours of culturing bulbs in these solutions, the pH of the solutions remained unchanged. In another set of experiments, 2%, 4% and 8% solutions were used after the pH of the solutions was raised to 7 by addition of a NaOH solution. Differences in the results between the two sets of experiments will be described presently.

The first externally visible effect of the treatment was that the growth of all treated roots was markedly suppressed. From the comparison of amounts of growth in several roots treated with 0.05%, 0.5% and 4% solutions for 24 hours, it was found that the greater the concentration of the solution, the less the growth. It was also found that in many of the treated roots retardation of growth was followed by death. The older roots showed, earlier in the treatment, a slight constriction in the region of elongation just behind the meristem. This became gradually more pronounced and at the same time, the older regions became progressively constricted until finally the entire root above the growing point became very thin. The meristematic region of these roots remained unchanged

in size, but the number of dividing cells in this region gradually decreased as the roots became more constricted. Finally the cells ceased dividing entirely. The constriction appeared earlier and the roots died more quickly in the more concentrated solutions. For instance, in an 8% solution, the constriction appeared in three or four hours and the roots died a few hours afterward. In a 1% solution, it took much longer before the constriction was recognized and several hours elapsed before the meristem ceased to show cell divisions.

In the neutralized solutions, the growth was suppressed as much as in the solutions of lower pH, but the constriction did not appear in any of the treated roots and none of them died even in the 8% solution which, if not neutralized, would have killed all within about 10 hours. Changes in the morphology and mitotic behavior of the chromosomes, induced by the neutralized solutions, were essentially the same as those produced by the more acid solutions. This indicates that the effects observed in treated roots are not due to an excessive concentration of hydrogen ions in the solutions. In a few preliminary experiments with *Vicia faba*, it was found that in 2% and 4% solutions the constrictions appear in a few hours and subsequently the roots die even in neutralized solutions. Evidently there are genetic variabilities in susceptibility to the action of sodium ribose nucleate.

Altogether about 350 roots were treated with solutions of various concentrations. Of these about 250 were excised and smeared directly from the solutions and the rest were left attached to bulbs and returned to tap water. Some of these roots were kept in water for eight hours and others for 24 hours or longer before they were cut off and smeared. The roots which took the full effects of the treatment did not regain a normal rate of growth in tap water and the chromosomal abnormalities persisted in these roots.

The roots treated with 0.05% and 0.1% solutions were completely normal except for a slight reduction in growth rate even after 24 hours of treatment. The roots treated with higher concentrations showed a slight effect on the chromosome morphology even after a few hours, and the full effect on the morphology as well as on the mitotic behavior of the chromosomes in five to eight hours, depending upon the concentration of the solution. From the study of all treated roots it was found that the effects are qualitatively alike in all effective concentrations but are quantitatively different in different concentrations and times of treatment. The best concentration and time of treatment to obtain full effects in a large proportion of dividing cells in onion root tips are exposure to a 2%-4% solution for between 8 and 16 hours.

In root tips which are fully affected by the treatment, chromosomes are to a greater or less extent shortened in length and increased in diameter at the metaphase (Figure 4*A*). The primary constriction at the kinetochore and the secondary constriction in the trabant-bearing chromosomes of these condensed chromosomes appear as clear, narrow gaps (Figure 4*A*). Since the early prophase chromosomes are not noticeably shorter than the untreated ones of the same stage, the extreme condensation must occur during the late prophase. It is of interest to note in this connection that the coiling of the chromatids is clearly visible in most of the prophase chromosomes and in the metaphase chromosomes which are not excessively condensed (see Figure 5*A*). Furthermore, in a number of prophase chromosomes each of the sister chromatids was found to be already split. The details of these particular aspects of the effects will be described and discussed elsewhere by Professor Huskins.

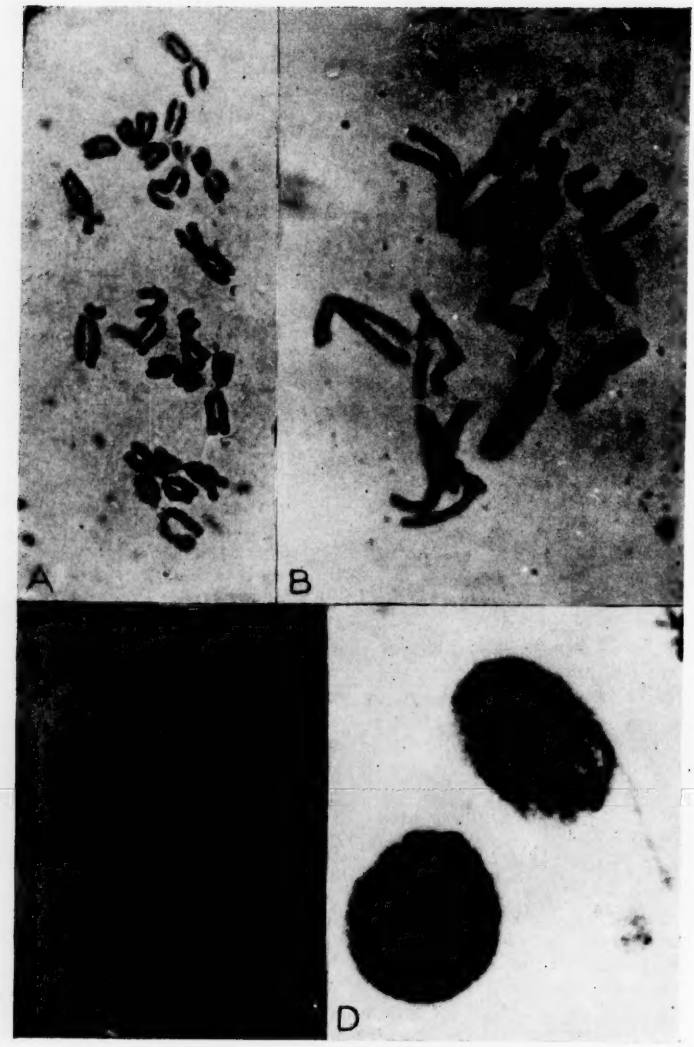
Most of the prophase chromosomes have been found to bear numerous "hairs"; and to resemble closely in appearance the lampbrush chromosomes of the vertebrate ovocytes. Some of the metaphase chromosomes are also "hairy" (Figure 4*B*). Although very similar in shape and appearance the "hairs" in the present preparations may not be related

in structure to those of the natural lampbrush chromosomes. The "hairs" in my preparations are Feulgen positive, whereas those in natural lampbrush chromosomes were shown by Duryee,[6] to be Feulgen negative. Feulgen positive lampbrush "hairs" have also been produced experimentally by treating the salivary chromosomes[6] and the ordinary mitotic chromosomes[10] with strong NaOH solutions. Although desoxyribose nucleic acid is present in both cases, as indicated by the positive Feulgen reaction, the "hairs" produced by the action of alkali and by the ribose nucleate solution are possibly not of the same nature, being in one case the product of direct chemical action of OH ions on the chromosomes; and in the other they are more likely to be the result of the physiological response of the nucleus to the disturbed cellular conditions induced by the ribose nucleate.

In some of the metaphase chromosomes, the arms of the sister chromosomes may be far apart while the kinetochores are not yet split (Figure 5*A*), and the "hairs" are invariably absent in these chromosomes. The "hairs" are visible, however, while the arms of the sister chromosomes are still closely associated with each other. It seems from these observations that the falling apart of the arms of the sister chromosomes is in some way related to the sudden disappearance of the "hairs," but what this relationship is, is not clear.

In many of the metaphase chromosomes, the splitting of the kinetochore is unusually delayed, and the X-shaped figures (Figure 5*A*) similar to those found in colchicine-treated root tips are found (see Levan,[8] for similar figures in onion root tips treated with colchicine). Although delayed, the splitting does occur and the sister chromosomes may be found completely separate and lying closely side by side (Figure 5*B*); or they may be scattered in the cells (see Figure 5*C*) and also Nebel and Ruttle,[9] for similar figures in colchicine-treated material). In some of the treated roots, over 10% of the dividing cells have shown delayed splitting of the kinetochore and scattering of the anaphase chromosomes in the cell; but in most, if not all of these cells, the chromosomes move apart to the poles and cytokinesis follows. The distribution of the chromosomes in the anaphase is frequently irregular, however. Thus, one or more chromosomes may be slower in movement than the others. They may even be left on the metaphase plate, while others are already at the poles. In other cells the chromosomes may separate in unequal numbers. Cases of the latter type of irregularity that have been precisely analyzed show distribution of 12:20 and 13:19. A number of other anaphase figures have been found in which the two groups apparently differed in chromosome number but an accurate analysis was impossible because the chromosomes were too closely grouped together. Some of these might represent other possible unequal distributions. It is clearly evident from the accurately analyzed cases that unequal distribution, possibly at random, of the 32 chromosomes occurs, giving rise to cells with higher and lower numbers of chromosomes than the diploid. This the author considers to be due to random movements of sister chromosomes to the poles; that is, it is a matter of chance whether the sister chromosomes move together to the same pole or separate to go to opposite poles. In such a situation, it would be expected that all 32 chromosomes would move together to the same pole only with extreme rarity thus giving rise to a tetraploid cell. So far no tetraploid metaphase has been found even in material exposed to 72 hours of treatment in the solutions followed by return to tap water. This is probably due to the extreme rarity with which this would occur by chance. It may be added here that in all roots which took full effects of the treatment, metaphases are present in large numbers while anaphases are much less frequent than in untreated roots. Actual counts made in a few roots showed that among all the dividing cells 41% were at the metaphase and 5% at anaphase, the rest being mostly prophases.

Besides the unequal distribution of the



"PAIRING" AND COLCHICINE-LIKE METAPHASES

Figure 5

The effects of the sodium ribose nucleate solutions on the chromosomes of the onion root meristem. *A*—Metaphase chromosomes with the arms already split and widely separated but the kinetochores not yet split; note the chromonema coils in many chromosomes. (4%: 12 hours). *B*—A configuration of chromosomes resembling that of the colchicine "metaphase"; note the "pairing" of the sister chromosomes (4%: 16 hours). *C*—Anaphase chromosomes scattered over the cell and not in poleward movements (4%: 16 hours). *D*—A large nucleus with a chromosome "tail" and a micronucleus at the opposite end of the cell; note the comparable size of the larger nucleus and a diploid nucleus at the lower left corner (4%: 12 hours). See text for details.

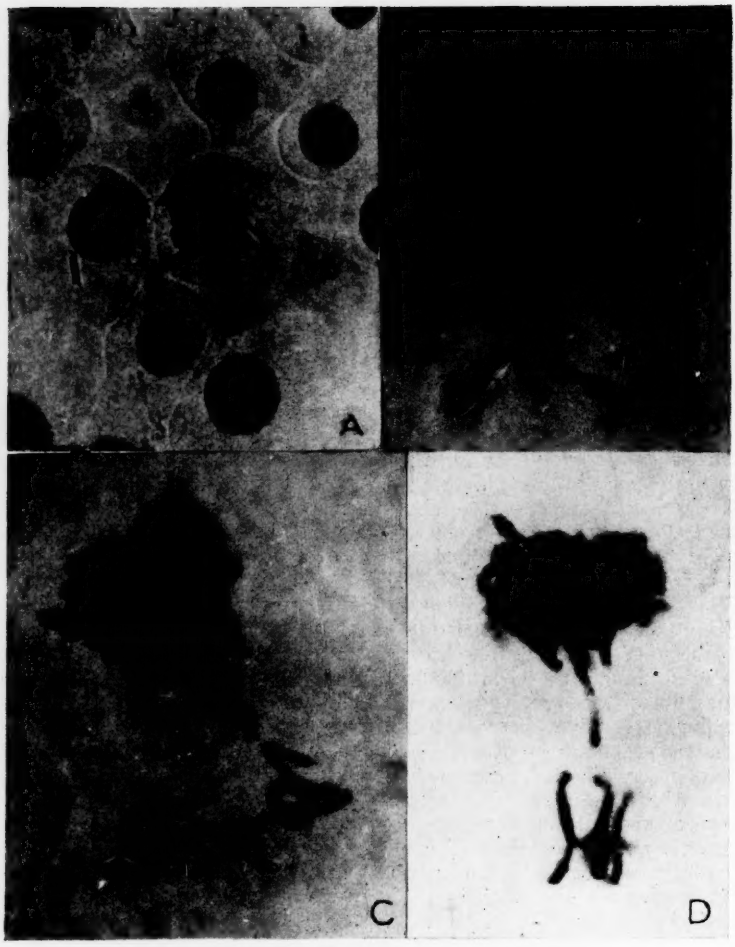
type just described, there has been found another type of abnormality in the chromosome distribution in the same root tips. This is illustrated in the elongated cell to the right in Figure 5*D*, which contains a large and a very small nucleus. The larger resting nucleus is approximately equal in size to the normal diploid nucleus in the neighborhood. The micronucleus at the opposite pole in this cell contains a very small number of chromosomes, probably only a few. If 32 chromosomes were involved in the unequal distribution in this cell, the number of chromosomes in the larger nucleus would be close to 32 and its size should be much larger, instead of being approximately the same as the normal diploid nucleus, as it actually is. It is evident, therefore, that 16 chromosomes instead of 32 were distributed unequally to the poles in this cell. A number of cells at the anaphase stage showing unequal distribution of 16 chromosomes have actually been found. In Figure 6*A-D* are shown 0-16, 2-14, 3-13 and 5-11 distributions. Other distributions have been found also. In the telophase, the smaller groups of chromosomes form micronuclei, when the chromosome numbers are very small, and in the resting stage following cytokinesis, these nuclei become heteropycnotic.

Careful observations of these 16 chromosomes which are undergoing the second type of unequal anaphase distribution have revealed that these chromosomes consist of strands which are the same in number and size as those of the anaphase chromosomes in the untreated root tips. This inevitably means that these chromosomes had not reduplicated since the anaphase of the previous cycle. Unreduplicated metaphase chromosomes, 16 in number per cell, have been also found. Evidently being unable to split into sister chromosomes, these 16 chromosomes have moved to the poles at random.

In many anaphase cells, particularly in those with unequally distributed chromosomes, one or more chromosomes are delayed in movement. This is illustrated in Figure 4*C* and 6*B*. In addition to lagging chromosomes, there have been found in the same cells and in different cells one or more akinetic fragments (Figure 4*F*). These fragments are of different lengths, but are composed always of the same number of strands as the other chromosomes in the same cell. In Figure 4*F* the main body of the chromosome from which the fragment is separated can be partly seen as a protrusion from the telophase nucleus at the left. The cause of the chromatid breakage in the formation of these fragments will be discussed later.

In many of the fully affected roots, a number of late anaphase cells have been found showing one or more chromosome bridges between the two groups of chromosomes (Figure 4*D*). These bridges are formed by the sister chromosomes which have moved apart to the poles but stuck together at the very tips of their free ends. In most of the cases, these chromosomes separate before the anaphase stage terminates, but in some cases they remain attached until the cell plate breaks them apart. In these cases, the breakage might not be exactly at the points of attachment: then one chromosome with a terminal duplication and another with a deletion might arise.

In the roots treated with 8% solution at pH 7 for 20 hours, a number of metaphases were found in which the chromosomes are contracted far more than in those treated with less concentrated solutions (Figure 4*E*). In some instances many of the chromosomes are almost spherical and the primary and secondary constrictions are not visible (note these features in Figure 4*E*). These chromosomes also show the lampbrush-like structure. Furthermore, the nuclear membrane seems to be still present in these cells and the chromosomes are all lying closely against it. The membrane disappears later and the chromosomes, after splitting, move apart to the poles as in normal mitosis. In addition to these abnormalities, there have been found a large number of cells in which the chromosomes are in a more or less compact mass due apparently to



EFFECTS OF TWELVE HOURS' TREATMENT

Figure 6

The effects of sodium ribose nucleate solutions on the chromosomes of the onion root meristem. All treatments comprised exposure of the roots to a 4% solution of sodium ribose nucleate for twelve hours. *A*—A cell at the late anaphase with all 16 chromosomes at the same pole; this is the 0-16 distribution of 16 undivided chromosomes described in text. *B*—2-14 distribution of 16 undivided chromosomes. Note that at the pole with 14 chromosomes one chromosome is moving behind the others. *C*—3-13 distribution of 16 undivided chromosomes. *D*—5-11 distribution of 16 undivided chromosomes.

their extreme stickiness. A similar abnormality was found also in the roots treated with less concentrated solutions, but in a much lower frequency.

The physiological mechanisms underlying the various effects of the ribose nucleate solutions on the meristem cells cannot be discussed in detail at this stage of the investigation. But it does seem appropriate to consider the physiological nature of some of the outstanding effects. It was noted above that the growth is markedly suppressed in all effective concentrations of the ribose nucleate solutions. This means that the rate of cell division in the meristem is considerably reduced. However, from the examination of root tips cultured for various lengths of time (8, 12 and 16 hours) it was found that the proportion of dividing cells to all cells in the root tips is approximately the same regardless of the time of treatment. Furthermore, this proportion is also about the same as that in the normal root tips growing in tap water. This must mean that the duration of the mitotic cycle is enormously prolonged by the treatment. In tap water it is about four hours[4]; in the present experimental solution it must be considerably longer than that. It was also observed that the proportion of cells in metaphase is increased with respect to the cells in other stages as the treatments are prolonged. For instance, in root tips treated with 8% solution for six hours, about 25% of all dividing cells are in metaphase, while in roots treated with the same solution for 19 hours, the percentage is nearly doubled. It is apparent, therefore, that the metaphase stage is prolonged considerably more than the other stages. Moreover, since the proportion of the dividing cells to the total number of cells in the roots does not appreciably increase, the number of cells that enter into the divisional phase must be very small.

Among the various effects of ribose nucleate solutions on the chromosomes, probably the most interesting are the inhibition of chromosome reduplication and the formation of akinetic fragments. These two effects seem to be closely related to each other. A breakage that causes fragmentation of the chromosomes is probably initiated some time before the fragment is observed as such, probably when the chromosome reproduces. At this time a replica of the chromosome is formed along its entire length, except at one point which will appear later as the point of breakage. Fragmentation would then be due to a partial inhibition of the chromosome reduplication. For a similar type of fragments found in the pollen grain of *Tradescantia* treated with mustard-gas vapor, Koller[7] offers a similar explanation for the cause of the breakage. He believes that the inhibition of reproduction is due to inactivation of a locus as the result of chemical combination of the locus with the mustard gas molecules, and a consequent inhibition of reduplication or polymerization of the desoxyribose nucleic acid. We will discuss later whether or not this hypothesis can adequately explain the present case.

A consideration of the cause of the reproductive failure in the treated chromosomes raises a question as to the nature of the component in the ribose nucleate solution that exerts this and other effects on the chromosomes. Zittle[12] studied the substrate activities of five different commercial products of sodium ribose nucleate (including that of the Schwarz Laboratory). He found that these products invariably contain a large quantity of polynucleotides but very little of the tetra-nucleotide or mono-nucleotide. From the consistently low content of mono- and tetra-nucleotide in all the different products, it can be assumed that the ribose nucleate used in the present experiment is very closely similar to the samples analyzed by Zittle.

In an attempt to determine what component of the sodium ribose nucleate solution is responsible for the various effects, four different mononucleotides of ribose nucleic acid are now being used in tests with onion roots. Complete results will be reported later. However, a preliminary result of the experiment with adenylic acid can be presented here.

In the onion roots treated for 18 hours in a 1% solution of this nucleotide, in the manner similar to that of the previous experiments, it was found that the growth is suppressed, a constriction is formed in the region above the meristem. The morphology and mitotic behavior of the chromosomes in the meristem is also changed in somewhat the same way as in the ribose nucleate solutions. Detailed examinations of the chromosomes in the meristem of these roots have shown the following effects: unusually high condensation, lampbrush structure, anaphase bridges, earlier splitting of the sister chromatids in prophase and scattering over the entire cells during anaphase. Delayed splitting of the kinetochore, fragment formation and the random distribution of the chromosomes have not been found. Apparently the kinetochores always split in time and the chromosomes always reduplicate. In contrast to the complete or partial inhibitory action on chromosome reproduction of the sodium ribose nucleate solutions, the adenylic acid is entirely devoid of such action. The delayed splitting of the kinetochore and the inhibition of chromosome reduplication are evidently due to some other substance. The possibility that this substance is a mono- or tetra-nucleotide seems to be excluded for the following reason. It was found by Zittle[12] that the commercial products of free ribose nucleic acid contain a large amount of acetic acid-soluble mono- and tetra-nucleotides. The proportion of the nucleotides in the purified product of Schwarz Laboratory was 28%, the rest being mostly polynucleotides. If the effects of the ribose nucleate solution were entirely due to tetranucleotides or to a certain mononucleotide, it would be expected that the root tips treated with a solution of free ribose nucleic acid would duplicate completely the effects of the ribose nucleate solution. Onion root tips treated with a saturated solution of free nucleic acid for 6, 12 and 18 hours did not completely duplicate the ribose nucleate effects but did duplicate those of the adenylic acid. This result indicates that neither the mononucleotides nor the tetranucleotides in the sodium ribose nucleate are able to delay splitting of the kinetochore nor to inhibit completely or partially chromosome reproduction.

The content of mononucleotides in the sodium ribose nucleate is very small, if there is any at all, yet it produces the effects that could be attributed to these low nucleotides. Either the amount of these nucleotides present is large enough to produce the effects or else they are formed from the tetra- and polynucleotides which the cells might have taken up from the solution. This latter possibility would depend upon whether these nucleotides are able to enter into cells of the root meristem.

According to Zittle, both the sodium ribose nucleate and the free nucleic acid contain large amounts of polynucleotides. It might, therefore, be that the effects produced by the sodium ribose nucleate which are not attributable to low nucleotides are due to polynucleotides. The fact that these few effects are not produced by the ribose nucleic acid could be explained by the insolubility of this compound in water.

A possibility that the effects of the ribose nucleate solution are due to an impurity seems to be excluded, because it was found recently by Mr. Irving Galinsky that a certain component of mononucleotides induces many of the same effects.

Tests for other components of the mononucleotide molecule are now under way and results will be reported elsewhere. However, the result of experiments with uracil, a pyrimidine base of ribose nucleic acid, may be reported here. This compound is only very slightly soluble in water; therefore, a saturated solution was used. Onion roots treated with this solution showed after seven hours of treatment a relatively high contraction of the chromosomes, lampbrush structure and a large number of chromosome bridges during anaphase. After 18 hours of treatment no further change in the morphology of the chromosomes was found. The growth of the root was not appreciably suppressed.

Whether other purine and pyrimidine bases can induce partly or entirely the same changes as the solutions of ribose nucleate and mononucleotide remains to be seen.

It is of interest to note that the chromosomes in many tumor cells are increased in number and show stickiness, clumping, etc.[1, 2, 5] Many of these abnormal features of the chromosomes in tumor tissues parallel those observed in the meristem cells cultured in ribose nucleate solutions. The close similarities in the chromosome abnormalities between these tissues and the fact that the nucleic acid content of the tumor cells is often greater than in normal tissue (see Stowell[11]) suggest that these abnormal features in neoplastic tissues may possibly be due to an excessive amount of nucleic acid.

I am gratefully indebted to Professor C. L. Huskins for his invaluable suggestions and criticism.

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SELECTION AGAINST RECESSIVE LETHALS

WRITING in *Science* (108:538-39), Curt Stern and Edward Novitski report a study of sex-linked lethals in Drosophila. This shows that the assumption of complete penetrance of the normal allele of a lethal is not correct. Actually in the material analyzed by Stern and Novitsky the female heterozygous for lethals tended to be less viable than homozygous normal sibs. In part the authors wrote as follows:

"The significance of recessive lethals for the dynamics of population is often considered solely in relation to their effect in homozygous or hemizygous state. The assumption is thus made that individuals heterozygous for these lethals are equivalent to homozygotes free from the lethal alletes. This assumption has been tested for 33 sex-linked lethals in *Drosophila melanogaster* and found to be incorrect for the majority of them.

* * *

"The sex-linked lethals consisted of 7 spontaneous lethals and 27 lethals discovered in low-dosage X-rays or gamma-ray irradiation experiments. A considerable number of these "experimental" lethals must be spontaneous ones which have arisen independently of the irradiation. All lethals occurred in an *X*-chromosome derived from the highly homogeneous Canton-S stock of *Drosophila.*

* * *

"A summary of the data is presented in Table I. If one excludes "doubtful" and sterile tests, one may calculate for each lethal a percentage of lethal-bearing among all adequately tested females. The amount of the percentage is, of course, subject to a statistical error. Taking the observed values without consideration of their individual errors, one would expect approximately equal numbers to fall above 50% and below 50%, provided the viability of the genotype heterozygous for any one lethal were like that of a lethal-free genotype. In addition, the spread of values above and below 50% should be identical within statistical limits.

"Actually, a plot of the viability values for the 33 lethals shows a two-fold asymmetry (Table 2) . . . These facts indicate that most sex-linked lethals tested have a considerable effect in decreasing the viability of females heterozygous for them.

"From the point of view of a population even a slight decrease in the viability of individuals heterozygous for a lethal should be of greater significance for its well-being than the loss of lethal homozygotes. In any given generation the frequency of homozygotes is defined by p^2—the square of the frequency, p, of the gene in the population—whereas that of the heterozygous carriers is $2p\ (1\text{-}p)$. For a rare gene (p being small and $1\text{-}p$ close to 1) the number of carriers may become hundreds of times as large as that of the homozygotes, so that a decrease in vigor of the carriers by, for instance, 5% will have a far greater effect than the complete elimination of the much rarer homozygotes."

TIMIRYAZEV AND LYSENKO

The Memory of the Great Liberal Russian Scientist Timiryazev Dishonored by Soviets

THE scientific authority of the late K. A. Timiryazev is frequently invoked in support of the official biological dogma associated with the name of Lysenko, which proscribes the Mendelian theory of heredity and which resulted in ruthless purges of Russian biological scientists beginning in 1936. Timiryazev was a distinguished, liberal Moscow professor of botany, very popular with Russian student youth. His name is borne by the oldest and most important Russian agricultural college, the former Petrovsk Academy, where he once taught. Timiryazev performed in pre-revolutionary Russia the same role that Thomas Henry Huxley played in England and Ernst Haeckel in Germany—that of an apostle of Darwinist science militant.

The use of Timiryazev's name by the Soviet oppressors of science is a cruel mockery of the memory of one of the best representatives of that progressive Russian scholarship which has written so many fine pages in the intellectual annals without any specious, nauseating boasts and xenophobia, such as currently fill the pages of the controlled press of the Soviet Union. It is true that Timiryazev said harsh things about Mendelism. But, as Dr. G. H. Beale well puts it: Timiryazev "saw no inconsistency in pointing out certain virtues in Mendelism," and admitted, in fact, that *"Mendelism removes the most dangerous objection which, in the words of Dawin himself, was made aaainst his theory."** (Beale's italics.) But, whatever comfort may be derived by Lysenko & Co. from Timiryazev's criticism of the Mendelian doctrine of genetics which is anathema to them — they can find no moral justification whatsoever for their activitv from the writings and teaching of the late Moscow savant.

On the contrary, had Timiryazev, who died in 1920 at the ripe old age of 77, lived today, he would doubtless be the first to condemn, unmercifully, the deeds of Lysenko, behind whom stands the high command of the Bolshevik party. He would condemn provided that the Bolshevik secret police would permit such an act of "disobedience," which is not at all likely. It is much more probable that Timiryazev, with his fighting temperament, would have been liquidated, as was another distinguished Russian scientist who opposed Lysenko—Professor Nikolai Ivanovitch Vavilov. For, Timiryazev was a passionate fighter for the freedom of scientific inquiry, for academic freedom and against personal monopolies in scientific research, for international comradeship of scientists—in short, for that intellectual liberty which is so essential to true scientific progress and which is being trampled in Soviet Russia today far worse than during Timiryazev's lifetime under the tsars. The fact that Timiryazev, a radical and a pacifist, joined, in 1917, that minority of the Russian intelligentsia which, out of misguided idealistic motives, sided with the Bolsheviks during the early so-called heroic period of the regime, when it was fighting for its very existence, does not invalidate what has just been said. Timiryazev did not change his convictions with regard to freedom and science, and did not live long enough under the Soviet system to learn from bitter experience its true totalitarian character.

There is ample evidence for these statements in the writings of Timiryazev, which were fortunately enough collected and published, without change, in Soviet Russia. Thus, in an article which appeared in 1904 in the famous liberal Moscow newspaper *Russkiya Vedomosti*, entitled "Academic Freedom — An Old Professor Thinks Aloud," and republished in 1939 in Vol. 9 of his collected works, Timiryazev emphasized the importance of the university self-

*Nature, Vol. 159, January 11, 1947, p. 152.

government, which meant the election by the faculty of the administrative officers, as a means of "securing of one of the fundamental and primary sources of free thought—the freedom of teaching." A prospect of "mental and moral corruption of whole generations of scholars, striving to guess what conclusions must be reached by their free science in order to be in agreement with the views of its bureaucratic censors," especially horrified Timiryazev. This is precisely what Lysenko and his bosses from the Politbureau are striving to accomplish today by methods that smack of medieval inquisition. Witness the forced renunciation of his theoretical views by Professor Zhebrak, of the Timiryazev Agricultural Academy in Moscow, who made the well-nigh fatal mistake of adhering to the doctrines of genetic science that are recognized by reputable scholars the world over.

What Timiryazev's reaction to this would have been can be gathered from a castigation of a colleague, who resigned in 1911 in company with 124 faculty members of the University of Moscow (including Timiryazev, himself) in protest against the interference of the reactionary tsarist Minister of Education with the self-government of the University, only to capitulate two years later. On his return to the University, this renegade spoke in his first lecture of the "error" committed by his 124 colleagues. Replying in 1914, Timiryazev wrote: "It is said that it is an 'error' to leave the University when all that is demanded of you is—'to bow lower to power whatever it is.' Englishmen, however, not wishing three centuries ago to bow to force, left their fatherland entirely and created a new free country overseas, and those who committed this 'error' are being honored to this day on one-half of the earth. And, when 150 years later Englishmen among those who did not 'err' decided again to reach out for those who left by 'error', there appeared among the latter an Englishman (he was called George Washington) who said, 'blood will either flow in this country or it will be inhabited by slaves; it is a terrible choice but who could vacillate.' His choice, of course, was an 'error', but the people shared his 'error' and history sustained it . . . In the course of centuries Englishmen became accustomed to the idea that everything is possible, that it is possible to leave one's country, to lose one's life; but one thing that is impossible is slavery, or what is even more shameful, servility. That is why modern Englishmen are not forced to 'leave' their universities."

These and other writings of Timiryazev underline the grave decline in intellectual liberty in Soviet Russia, as compared even with the tsarist regime. In tsarist time, Timiryazev could protest in the press (there *was* an independent press in tsarist Russia), and otherwise, without being liquidated. A professor at a State University could resign in protest against the arbitrary actions of the administration and betake himself to some one of the privately endowed institutions, which began to spring up in Russia in the early years of the century, or he could accept, quite legally, a professorship abroad without becoming thereby a traitor to his country, as would be the case at present. For instance, Mechnikov, the Nobel prize winner, found refuge at the Pasteur Institute in Paris, Paul Vinogradov, the eminent historian, at Oxford, and there were others. They were never barred from visiting their native land, in fact, they were always welcome visitors of whom all educated Russia was very proud. That an official dogma à la Lysenko or Zhdanov could be set up for every scientist to follow in his university teaching and research, was simply unthinkable; not only in natural but also in social science. Even teaching of economic theory from a Marxist standpoint in pre-revolutionary Russian institutions of higher learning was not uncommon.

The present degeneration of intellectual liberty indicates, by the same token, how misleading is the assertion, frequently made without serious qualifications, that western conceptions and traditions of freedom have been alien to the Russians. They were not alien to the

generation of Timiryazev and many younger men and women who fought and made great sacrifices for the cause of liberty—sacrifices that were by no means fruitless. A serious retrogression has occurred during the last 30, especially the last 20, years. But, what was lost, let us hope, will be more than regained some day in the not too distant future. Then the memory of Timiryazev will be truly honored by his legitimate heirs—the free scientists of Russia—and not dishonored by tributes from their oppressors.

L. V. SVOBODIN

(L. V. Svobodin is the pseudonym of a Russian scholar and student of Russian affairs who has lived in the United States many years.)

✦

STUDY OF SALIVARY GLAND CHROMOSOME WITH RECORDING MICROPHOTOMETER

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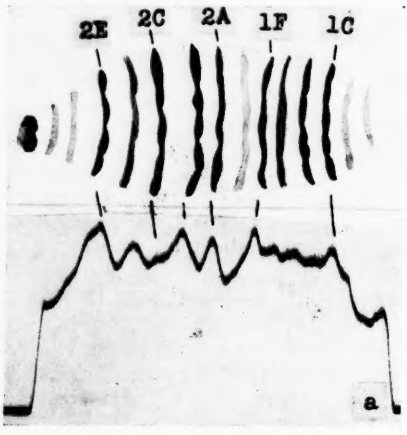
THE recording microphotometer is an instrument used by optic physicists for examining the intensity of a beam which passes through a slit. The intensity is measured by the effect of the beam on a photographic plate. If a translucent object is placed in the path of the beam, the intensity is reduced, and this reduction can be measured by the changing deflection of a galvanometer. The deflection is recorded automatically as a graph. This instrument can be used for making out the minute structure of the salivary gland chromosome of dipteran larvae. Since the number and the relative staining capacity of the bands of the chromosomes are more accurately shown than by simple observation under the microscope, this method is more objective than vivid observation. Even the presence of a very faint band, which is hard to discriminate under the microscope, may be indicated by a slight rise of the curve.

In Figure 7 is shown a graph obtained by this method from a preparation of the sixth salivary gland chromosome of *Drosophila virilis,* together with a sketch of the same chromosome in the same preparation. The bands are represented in the graph by crests of which the height shows their density. The corresponding bands and crests are connected by lines. To obtain results by this method, the chromosomes must be straight; a crooked chromosome is very hard to operate on. The graphs obtained for different preparations may not be exactly the same, but, if the density of the bands is classified roughly into three or four grades, practically identical results may be obtained. It is to be noticed that, as shown in Figure 7, there are some discrepancies between the sketch and the graph in details. It is very hard to tell which shows the reality. At any rate, this method seems to be useful for checking the visual observations.



VISUAL AND METERED MAPS

Figure 7

The height of the crests in the photometer chart is proportioned to the density of the bands.

APPLICABILITY OF MODERN GENETIC CONCEPTS IN THE MANAGEMENT OF SCHIZOPHRENIA*

FRANZ J. KALLMANN

IT is a curious commentary on certain imperfections of human nature that genetic theories, when applied to our own species, are often subject to an amazing variety of illusive distortion and partisan abuse. In many discussions about possible practical applications of the principles of organic inheritance in man, *ad hoc* assumption and emotionally conditioned *innuendo* tend to take the place of the more pedestrian approach of fitting relevant facts into useful hypotheses. Instead of testing the potential applicability of factual genetic data in the clinical management and future prevention of certain forms of mental disorder, psychiatric field-workers have been inclined to consider heredity as "a study of one's uncontrollable ancestors."

By thinking in such convenient and still rather popular cliches, one might be tempted to dispose of the problem of using genetic concepts in the treatment of schizophrenics by the following simple argument:

Behavioral patterns can be divided into two types of reaction, normal and pathological. Normal behavior is a quality which is usually desirable. It is found, or to be expected, whenever outside conditions are satisfactory or, more precisely, when circumstances prevail which we are inclined to classify as favorable. By definition, therefore, normal behavior patterns become identical with what we consider to be favorable environment.

With regard to pathological reaction types, a distinction may be made between reversible and irreversible patterns. If one postulates that pathological changes due to external causes tend to be reversible, one might say just as well that most changes found to be reversible (with or without treatment) are caused by environmental influences.

Proceeding on this premise, it would seem safe enough to ascribe all apparently irreversible changes to influences which cannot be controlled *because* they are hereditary. Again simply by definition, all the traits produced by heredity become disagreeable conditions which are bound to remain entirely refractory to therapeutic management.

In an argument about the questionable validity of such a possibly too arbitrary definition of heredity, it seems comforting to know that one can always throw in some casual reference to the demoralizing aims of geneticists and to their unfortunate connection with the depressing fact that there are still so many defective and maladjusted people among us. With more liberal financial aid from well-heeled and optimistic organizations, and with less interference by the influential in-laws of misanthropic geneticists, we might envisage the uplifting of idiots to the level of genius, and of frustrated mediocrity to that of superhuman specimens. But to the regret of all of us, there simply does not seem to be enough money in this world to achieve this truly philanthropic purpose.

The Ability to be "Normal"

In a more realistic approach to the genetic problems of human personality disorders, it is legitimate to assume that basically uniform patterns in the organization or disorganization of *mental capacities* are controlled by heredity in the same manner as are those underlying the normal or abnormal development of physical traits. From a genetic standpoint, the capacity for maintaining a

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state of mental health is a complex biological phenomenon. It cannot be attributed merely to the providential absence of emotional strain exercised by the prevalence of social imperfections in the structure of modern society. At all times, this capacity to maintain mental health constitutes an integral part of human personality development and is a central driving force of the normal human being. The drive to exist rests upon the individual's ability to conduct a multitude of psychosomatic functions with a relative degree of vital efficiency.

Despite the rather dogmatic claims of some modern evolutionists, the *biological process of personality integration* never ceases to be subject to the laws of organic existence and of structural growth. No aspect of this developmental process can be assumed to occur either by chance or by instinct. Differences in terminology do not alter the fact that the possession of instinctive energies at birth depends on the capacity for maintaining organic life, which must have begun to function before it lends itself to interpretation as to its psychological meanings and social consequences. Beyond question, there could be no vital energy in any infant unless it had been produced by the operation of a complicated genetic process. It is equally certain that no evidence is available to support the concept of a self-perpetuating form of human culture that could exist in a biological vacuum, or to imply evolutionary differentiation of behavioral responses without the organic means of expressing behavior.

Behavioral Plasticity

For the purpose of descriptive convenience it is perfectly legitimate to distinguish, as Dobzhansky and Ashley-Montagu[2] do, between instinctual generality and acquired specificity of human behavior, or between the separate effects of organic and social inheritance, or between specialized fixity and adjustive plasticity of mental traits. Psychologically oriented biologists may also be correct in stressing that behavioral plasticity of the human mind represents the most typical and uniquely human characteristic. There are no intransigent objections to such a generalized formulation, even if one may find it difficult to concede that "social organizations on the human level are built on the principle that an individual is able to alter his behavior to fit any situation, whether previously experienced or new" (as has recently been claimed by the same group of writers). In fact, human personality development is so intricate a process that it permits description of the multiformity of its existential expressions on many organizational levels of appearance in the organic world in accordance with Hoskins'[3] concepts of biological integration.

Genetically, however, there are definite limitations to the candid or disguised tendency to think of behavioral responses of man preeminently in terms of *culture-personality problems* "emancipated from dependence upon inherited biological dispositions." Regardless of the degree of evolutionary emancipation achieved, mental behavior of any kind remains a structural function of the organic nervous system. The ability to be mentally adjusted, as well as the ability to react to "unadjustable" circumstances with a true psychosis, must be regarded as a unique expression of the attainment of human status in the evolutionary development of man's mental equipment and cultural setting. These abilities depend basically on the common denominator of hereditary potentialities, since it can be shown without difficulty that similar mental reactions of a normal or psychopathological variety are produced by similar environmental circumstances only in a certain number of the persons exposed to them. One may say that the tendency to become vulnerable to the destructive effect of a schizophrenic (or other) psychosis, and also the capacity to maintain a mentally adjusted life despite biological and cultural imperfections, are both independent indications of the genetically controlled inability of man to attain superhuman status, emancipated from the bondage of organic inheritance.

Genes and "Fate"

This statement does not mean, of course, that a person is "born" a schizophrenic, or that all carriers of the schizophrenic genotype will actually develop the trait as a matter of fate. From a genetic standpoint, the term "hereditary" applies to any mental disorder that would not originate without the presence of a certain gene or combination of genes. The implication is that some persons *have* the genetic capacity for reacting to precipitating stimuli with a schizophrenic type of psychosis, while others *have not* this capacity. Whether or not a real psychosis will be developed by such a "predisposed" person usually depends on an intricate interplay of constitutional and environmental factors.

The action of *environmental agents* may be instrumental in bringing such a psychotic state to expression, but it should not be assumed that the suppression of an unexpressed, or only mildly expressed, genotype must necessarily be due to the action of purely environmental influences. Very frequently, protection afforded by other genetic background factors in a person distinguished by a strong constitution may be more important than the accidental absence of deleterious elements in the environment. In any case, there is no known constellation of purely environmental circumstances that would produce a true schizophrenic psychosis in a person who does not have a specific predisposition for the condition. The tendency to disregard this easily demonstrated principle merely serves to obscure every possibility of applying a genetic approach to diagnosis and therapy.

In schizophrenia as well as in other inherited disorders, the rationale of any treatment depends on the etiology of the disease we are treating. If it can be shown that the development of a certain type of mental deviation cannot be explained without a specific dysfunction produced by genetically controlled elements, a more profound knowledge of these agents is bound to lead to improved methods of treatment rather than to a fatalistic state of therapeutic inactivity. The persistently maintained analogy of inheritance and incurability is merely a reflection of deep-seated general preconceptions and rationalizations which still prevail in relation to the implications of heredity. Unfortunately, even many intelligent and academically trained people have been unable so far to acquire complete immunity from one of the most obdurate of modern taboos.

Generally speaking, there is no inherited disorder which is incurable merely because it is hereditary. With respect to *symptomatic* therapy, the contingencies of inheritability and curability are virtually unrelated and certainly not mutually exclusive. A depression may clear up spontaneously or it may respond to shock treatment regardless of whether it has been predominantly reactive or endogenous in nature. An encephalitic personality deviation acquired in childhood may remain incurable, while a eunuchoid condition will lend itself to active hormonal therapy despite its possibly genetic origin. The effect of anticonvulsant drugs is considered to be independent of the etiologic type of epilepsy treated, and no one will claim that the knowledge of the genetic basis of schizophrenia has interfered either with the discovery of shock treatment or with any aspect of its clinical application. By analogy, there is not the slightest genetic reason militating against the development of some new compound that would correct certain biochemical deficiencies in manic-depressive psychosis or amaurotic idiocy.

The Genetic Approach to Therapy

In fact, as far as the prospects for a *causally directed* treatment of such disorders are concerned, a better understanding of their respective genetic background factors is certain to be of immediate therapeutic value. Since we cannot expect to find a cure for a clearly inherited condition through the simple device of minimizing the effect of heredity in regard to human mental capacities, it is essential to determine how the un-

derlying dysfunction is transmitted, reproduced, and brought into play.

In general one may say that therapeutic action against an inherited disorder is possible through several approaches. We may either modify—perhaps through substitution—the biochemical dysfunction which is the primary effect of the underlying principal gene or genes, or we may change the expression of this genotype through methodical stimulation of secondary modifiers. In addition it may be possible, through carefully directed management, to modify vital environmental factors. For all of these purposes it is necessary that we know how a morbid genotype is chemically structured, under which conditions it is likely to be fully expressed, and to what extent its expressions may be controlled by constitutional resistance factors.

Even if a severe anomaly is produced by one very potent gene whose *penetrance* and *expressivity* are practically complete under ordinary circumstances, it does not follow that the therapeutic situation would necessarily be hopeless. Beadle's experiments[1] in *Neurospora* have shown how the components from which a given protein molecule is constructed must themselves be synthesized. One or more steps removed from the final act of protein elaboration, such a synthesizing process depends on enzymes which in turn depend on other genes. Therefore, any reactions by which biochemically essential compounds are synthesized can theoretically be interrupted by the induction of mutations in the genes concerned. Unfortunately, there is as yet no known way of directing mutation-producing agents toward specific genes, although it is no longer questionable that artificial gene mutations can be obtained at will by the use of ultraviolet light, mustard gas, X-rays, and other radiation. The controlled production of specific shielding mutation remains a possibility.

Therapeutically it is of definite advantage that the more common mental disorders controlled by specific inheritance factors are known to have a rather wide *range of variation* in expressivity. This is especially true for the variably manifested conditions of the genetically specific disease entity, schizophrenia, which serves well to illustrate the extent to which the intricate interaction of heredity, constitution and environment is important in therapy.

Even without the corroborative evidence obtained by the observation of twin pairs and other groups of blood relatives, it is generally known that the variations in the clinical manifestation of the single-recessive unit factor for schizophrenia range from the mildest to the most destructive forms of the disease. The clinical variations include the episodic syndromes of a simple or catatonic variety, as well as the chronic and strongly progressive forms with a paranoid or hebephrenic coloring. It is especially important that the expression of the schizophrenic genotype may be completely suppressed under certain conditions. Such genetically "frustrated" homozygotes may be either schizoid in personality or completely normal in outward appearance.

The genetic evidence for this marked variability in the expression of the schizophrenic genotype concurs with the routine observation that schizophrenic phenomena occur in different types of people, at different ages, and under widely different circumstances. The practical implication is that schizophrenia, although plainly based on a specific predisposition, can be both prevented and cured. Therapeutically, the most effective procedure would consist in a true duplication of the *biological defense reactions* whereby a strong constitution protects a homozygous carrier of the schizophrenic gene combination from developing a progressive psychosis. The fact is definitely established that some schizophrenic processes may either be arrested spontaneously or thwarted completely. From this it follows that whatever takes place in the mobilization of constitutional defense mechanisms of such persons can be identified morphologically and somehow duplicated biochemically. It is safe to predict that the therapeutic problem of schizophre-

nia will be near its final solution, if it can be determined why some monozygotic co-twins of schizophrenics develop no psychosis although they live under comparable environmental conditions; or why they do break down with a milder psychosis at some other time; or why they may show a more favorable type of response to the same method of therapeutic stimulation. In all future twin studies, the emphasis should be on the "why" rather than on establishing the fact itself.

Schizophrenia and Physique

From the standpoint of treatment, it seems highly essential that the degree of constitutional resistance to a schizophrenic predisposition is somehow correlated with the morphological development of *mesodermal* elements as measured by the athletic and asthenic components of physique and by significant differences in the ability to maintain a stabilized level of body weight.

In a recently studied test group of 400 single-born schizophrenic males this relationship was explored. The group was classified biometrically as to somatotype by one team of investigators, and classified psychiatrically by another team. Statistical analysis of these data revealed that the strongest resistance to schizophrenic deterioration was found in patients with high athletic and low asthenic components of physique. The tendency to extreme deterioration corresponded to a high asthenic component, which was inversely related to the athletic component. No direct relationship was observed between degree of resistance to schizophrenia and variations in the pyknic component, the averages of which remained constant for the three divisions of the survey.

The same biological principle prevails in that relatively small group of monozygotic twin pairs whose behavior with respect to schizophrenia reveals some significant dissimilarity. If one twin remains completely free of schizophrenic symptoms or breaks down much later than the affected co-twin (or shows a far more benign type of psychosis), there is always a difference between the twins in regard to physical strength and body weight from early childhood. These differences in physique are consistently in favor of the more resistant twin. Accordingly, any factor adversely affecting either the general constitutional equilibrium or the stability of body weight may be expected to reduce resistance to the manifestation of schizophrenic phenomena, or may threaten the adequacy and permanency of a spontaneously or therapeutically established remission. The list of damaging factors observed most frequently in our twin material includes unusual physical or emotional strains, pregnancy, acute infections, or a drastic reducing diet. The clinical disregard of any of these factors may be responsible for the crucial difference between success and failure in the treatment of schizophrenia.

The stability of adequate body weight is apparently as important in relation to the maintenance of constitutional resistance to the schizophrenic genotype prior to the development of psychotic manifestations as an increase in weight tends to be with respect to the prospects of recovery during the acute stages of a schizophrenic psychosis. It is indicated by the weight curves of monozygotic twin partners remaining discordant as to schizophrenia that psychotic breakdowns in the constitutionally inferior twin are usually preceded by loss of weight below the level maintained by the more resistant co-twin, while clinical remissions are generally found to be associated with a temporary return to this level.[7]

The emphasis on a stable or increasing weight curve as an easily measurable indicator of the protective or recuperative power of the constitution does by no means imply that merely a gain in weight or excessive overweight might be able to cure schizophrenia. Of course, the correlated changes in clinical symptomatology and body weight are secondary expressions of basic biological processes, which play a role in both phenomena. The validity of this assumption is borne out by the observation that the weight curve frequently points to a change in the

course of the disease before this change is clinically recognizable.[8]

It is also evident that the therapeutic significance of this general biological principle is not invalidated by the occurrence of faulty and ineffectual overreactions in some old schizophrenics who were treated unsuccessfully. These patients go downhill in spite of, rather than because of, their overcompensatory gain in weight. It may be remembered that clinical recoveries do not occur in schizophrenic or tuberculous patients who are losing weight or who prove to be unable to regain weight lost in the incipient stages of the disease. One of the guiding principles in the management of schizophrenia should be, therefore, to keep a potential or recovered schizophrenic patient on a stabilized level of constitutional resistance.

Summary

The *general conclusions* to be drawn concerning the role played by heredity and constitution in the treatment of schizophrenia, may be formulated as follows:

No inherited disorder is, *per se,* incurable because it is hereditary. But such disorders cannot be cured through the simple device of denying the existence of human heredity. If the present methods of treatment of such disorders still happen to be inadequate, the therapeutic failure is due to insufficient knowledge about the nature and constitutional controllability of the basic genetic mechanisms producing an underlying biochemical dysfunction. In inherited disorders which are not fully expressed under certain circumstances, successful treatment may be possible. We may either render the given morbid gene less penetrant, or we may change its expression through carefully directed management of vital environmental influences or by methodical mobilization of constitutional resistance factors. If intensified genetic investigations lead to a satisfactory clarification of the ways in which resistance operates—and I cannot see how they could fail to do so—they will have aided substantially both in the understanding of schizophrenia and in its therapeutic management.

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